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COMPARISON OF PATCH AND CONTACT TEST RESPONSES IN CHROMATE SENSITIVITY

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IN chromate dermatitis, comments have arisen[6] concerning the following: (1) Do patch tests offer any explanation for the manner of acquisition, exacerbation and chronicity? (2) Do patch tests influence the number or degree of positive tests? (3) Does the presence of an acute or chronic dermatitis, especially if extensive, influence patch test reactions? (4) What is the optimum concentration of aqueous potassium chromate to be used for patch tests? (5) What degree of patch test reaction indicates a true sensitivity to chromates?

Information on these questions was sought by simultaneously performing patch tests and contact tests with different concentrations of chromate in persons known to be sensitive. Patch tests were done by the Elastoplast strip method.[3] The contact tests were done by moistening filter paper squares, 1 centimeter, with the respective dilutions and immediately placing them on the patient's back. They were allowed to dry in place. Nevi and bony points were used for identification. This method served to reproduce the manner of exposure—chromate solutions spalshing or wetting the clothing, gloves or footgear and then drying in contact with the skin. Drops were placed on the skin and allowed to dry in order to imitate splashing or wetting the bare skin. The results are recorded in Table I.

PATCH TESTS

Concentration.—These data are more evidence that 0.1 per cent aqueous chromate is sufficiently strong for detection of possible sensitivity. A concentration of 0.2 and 1 per cent can be used, but more intense reactions will occur. The degree of positivity is directly proportional to the concentration of the testing solution. The signs of reaction reflected from the

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TABLE I. PATCH AND CONTACT TEST FINDINGS IN CHROMATE SENSITIVITY

Cases Sex and Age	H. A. M—30	B. L. M—36	S. C. M—25	R. A. M—40	S. T. M—52	W. O. F—20
Patch tests—aq. potassium chromate						
Per cent						
1	not tested	erythema edema flaring vesicles weeping	not tested	erythema edema flaring	erythema edema flaring vesicles pustules weeping	not tested
0.2	erythema edema flaring	erythema edema flaring	erythema edema flaring	erythema edema flaring	erythema edema flaring vesicles	erythema edema flaring
0.1	erythema flaring	erythema flaring	erythema flaring	erythema	erythema flaring	erythema flaring
0.01	0	faint erythema	faint erythema	faint erythema	three pustules	faint erythema
Time for itching	6 hrs.	5 hrs.	7 hrs.	6 hrs.	5 hrs.	3 hrs.
Time for signs	less than 1 day	less than 18 hrs.	less than 16 hrs.	less than 1 day	less than 1 day	less than 1 day
Time for healing	16 days	20 days	15 days	14 days	24 days (loss of pigment)	14 days
Contact tests—aq. potassium chromate						
Per cent						
1	erythema	erythema edema vesicles	erythema edema vesicles	erythema edema vesicles	erythema edema pustules	erythema edema
0.2	0	erythema	0	0	erythema	0
0.1	0	erythema	0	0	0	0
0.01	0	0	0	0	0	0
Time for itching	5 hrs.	5 hrs.	7 hrs.	6 hrs.	6 hrs.	3 hrs.
Time for signs	10 min.	10 min.	10 min.	10 min.	10 min.	10 min.
Time for healing	0	16 days	16 days	14 days	16 days	10 days
Activation of previous sites of chrome dermatitis	0	0	0	0	0	0

least to the greatest degree are erythema, edema, flaring, vesiculation and/or pustules with or without weeping.

Time for Itching.—This is an estimate, three to seven hours, because it was determined by the subjects. Some could not tell which site started to itch first, the Elastoplast patch or the contact tests. Itching appeared after the onset of signs.

Time for Signs.—This was well established. All tests were positive in less than one day and no delayed reactions occurred.

Time for Healing.—This also is an approximation, fourteen to twenty-four days. Fading of erythema was taken as the end point. The time in *Cases H. A., S. C., R. A., and S. T.,* is fairly accurate because they were seen often enough after the tests to determine rather closely when the erythema began to subside. The degree of positivity of the test determined the healing time. A simple erythma (low degree) subsided faster than when it was accompanied by edema, vesicles and/or pustules (high degree). No topical treatment was used so these healing times can judge old or new therapies for chromate dermatitis.

CONTACT TESTS

Concentration.—Patch tests with 1 per cent aqueous potassium chromate induced far more severe reactions than when the same concentration merely touched the skin. Figure 1. Patch tests also produced reactions in much higher dilutions than contact tests. The principal finding to emerge is that

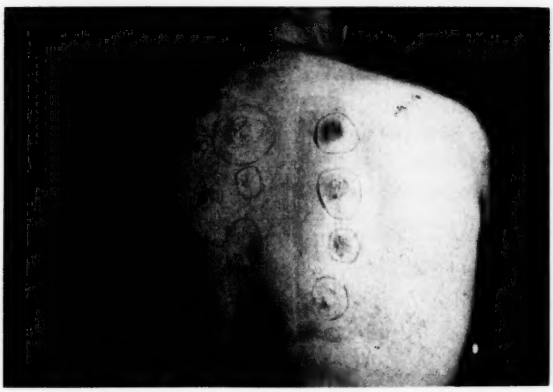

Fig. 1. Case S. T., is a white man, aged fifty-two. On the right are the patch test reactions, Elastoplast strip. Reading down, notice the embossed reaction to 1 per cent (1:100). There is still a similar response to the 0.2 per cent (1:500), and an erythematous, edematous reaction to 0.1 per cent (1:1000). This subject showed three pustules at the dilution of 0.01 per cent (1:10,000). To the left are the contact tests. The reaction to 1 per cent tends to duplicate the reaction to the patch test of 0.1 per cent. Erythema appears at 0.2 per cent with a plus-minus reaction to 0.1 per cent. This patient is a miner and operates a coal digging machine. On two occasions he was patch tested with paint scrapings from this machine, but negative reactions were obtained. When another recurrence developed, he was repatch tested with the paint scrapings, and this time the test was left on three days. A papular, pruritic dermatitis developed which flared over the entire outer aspect of the arm. This experience aroused speculation as to whether the period of contact, the temperature, and secretions from the skin may have chemically altered the chromate valence in the paint, which was suspected to contain zinc chromate, to a state inducing sensitization.

a positive test to 0.1 per cent serves to indicate a contact reaction to 1 per cent. Cases B. L., and W. O., had drops placed on their skin, and the same reactions developed as with the filter paper squares. Any aqueous concentration of chromates touching the skin directly or through clothing would, of course, be subjected to evaporation with rapidly increasing concentrations of chromate ions.

Time for Itching.—This is an approximation, three to seven hours. Knowing that symptoms appear quickly might prove helpful in detecting hidden sources of chromate contacts.

Time for Signs.—The first signs were seen when the filter paper squares started to dry, around ten minutes. Erythema was marked at 1 per cent and steadily faded to 0.1 per cent, and no erythema was noted in dilutions of 0.01 per cent. The presence of erythema at dilutions of 0.2 and 0.1 per cent did not dispose to eventual positive contact tests. The 1 per cent strength produced reactions, embossed in their appearance by the marked edema, erythema and vesicles. Each positive contact test developed in three to seven hours. Cases H. A., and R. A., when all test sites had healed, were again contact-tested with 1 per cent aqueous chromate on the flexor surface of the right arm. The reactions were slightly more severe and took longer to heal, perhaps due to the thinness of the skin in the arm. Their appearance would seem to preclude any influence by existing or developing positive tests to chromate.

Time for Healing.—These figures should further circumvent too much enthusiasm for topical treatment agents. The healing time was shorter than with patch tests, ten to sixteen days compared to fourteen to twenty-four days. Exacerbations of chromate dermatitis due to splashing or wetting the skin should require less healing time or mimic healing time of contact tests. Clothing, gloves or footgear becoming wet with chromate solutions should tend to mimic patch test healing time.

Activation of Previous Chrome Dermatitis.—The complete absence of any symptom or signs developing at previous sites of chromate dermatitis augers well for the safety of testing for chromate sensitivity.

CHROMATE REACTION IN PRESENCE OF EXTENSIVE DERMATITIS

Five patients comprise the findings on this question.

Case 1, a white male diabetic, aged sixty-four, had a generalized, exfoliating dermatitis of five years' duration. The tests were done on the upper back at an area of fairly normal skin. One per cent aqueous chromate induced a patch of bright erythema in which several pustules developed. The response faded in four to five days. It was considered a 1 plus reaction.

Case 2 is a white male, aged fifty-seven. He was hospitalized for an extensive, acute dermatitis. Patches of erythema developed from 1 per cent chromate, nickel chloride, gold chloride, silver nitrate, copper sulfate and 0.1 per cent mercuric chloride. They all subsided within a week. The reactions were considered to be about 2 plus. He refused testing after his skin was well.

Case 3, a white female, aged forty-seven, was seen in the hospital for an extensive subacute dermatitis. Chromate induced a patch of erythema which became papular in a few days and remained as an area of pruritic, papular dermatitis, persisting for three weeks. This reaction was classed as indicating typical chromate sensitivity.

Case 4, a white male, aged fifty-seven, was hospitalized for an acute, "explosive type" dermatitis. Chromate one per cent and mercuric chloride 0.1 per cent produced bright patches of erythema. The chromate reaction subsided in four to five days,

but the mercury reaction persisted almost two weeks. A month later, the tests were redone and only the mercuric chloride 0.1 per cent was positive.

Case 5, a white female, aged forty-three, had a subacute dermatitis affecting the upper and lower extremities. Chromate and gold chloride 1 per cent displayed patches of erythema. The gold reaction faded away in less than a week, but the chromate reaction went on to form a patch of papular dermatitis, persisting several weeks.

Cases 3 and 5 are considered true instances of chromate sensitivity. The deciding criterion was the persistence of the test reactions. Cases 1, 2 and 4 were designated as 1 to 2 plus reactions. They disappeared in less than a week. In Case 4, a retest after the skin was healed produced a negative test to chromate, but a repeat of the positive test to mercury.

CONCENTRATION OF CHROMATE FOR PATCH TESTS

During 1954, the procedure already described[3] for detection of metal sensitivity was carried out in an additional 243 patients. In no instance did 1 per cent aqueous chromate induce needlessly severe reactions. The presence of a yellow stain on the skin from the test, and having observed no erythema or delayed reaction from the stain, is good evidence that this strength for patch tests is not a primary irritant. The predominance of negative tests is more evidence that positive test reflects some degree of sensitivity to chromates. Skog and Thyresson[11] during the period 1948 to 1951 tested 8,005 patients who had been diagnosed as instances of eczema or dermatitis. They used 0.5 per cent (1:200) aqueous potassium bichromate. Pirila and Kilpio[7] believe that 0.5 per cent (1:200) is suitable for testing, and that in general it does not produce toxic reactions. Schwartz and Dunn[10] investigated an increase in the incidence of dermatitis in a woolen mill which resulted from a change in concentration of the mordanting solution of sodium dichromate in the dye bath from 0.5 to 3 per cent. A 3 per cent aqueous dichromate was used for testing. The exposure to 3 per cent chromate produced chrome ulcers in some workers and chrome sensitivity in others who had not been previously affected when exposed to 0.5 per cent (1:200) dichromate solution. This observation is important because increasing concentrations of chromates predisposed to a higher incidence of dermatitis. A parallel is seen in Table I; namely, the degree of reactions reflected the method of testing and concentrations used. Schwartz and Dunn[9] also used 3 per cent aqueous dichromate solution in studying dermatitis occurring among operators of air-conditioning equipment. Spier and Natzel[12] tested 1239 patients using 0.5 per cent (1:200) aqueous potassium bichromate. No misleading toxic reactions were noted. Sulzberger and Baer[13] recommended testing with 0.2 per cent (1:500) potassium dichromate in all patients suspected of having a cement dermatitis. A previous review[8] of concentrations of chromate recommended for testing disclosed variations from 0.1 to five per cent.

TESTS INDICATIVE OF TRUE CHROMATE SENSITIVITY

During 1954, thirty-four patients out of 243 tested were found to display positive patch tests to 1 per cent aqueous chromate. Fourteen patients out of thirty-four, or 41 per cent, let their reactions to chromate be known by a patch of erythema, or a 1 plus patch test reaction. The erythema did not appear acute; it was similar to the color of a nevus flammeus. It seemed to be deep-seated. The epidermis looked as if nothing had disturbed it. There was no itching. The erythema subsided within three to five days. Where it was possible to check the site after a week or so, quite often a few erythematous papules were found and these itched. The sex distribution in the fourteen cases was five males and nine females. The hands, hands and forearms were the usual sites of affection. Not one of the patients was in an occupation prone to inaugurate a chromate dermatitis. Twenty patients out of thirty-four showed 4 plus or eczematizing reactions to chromate. Nine males had their dermatitis on the hands, or hands and forearms. Ten of eleven females had their hands, hands and forearms, or hands and feet affected. The sex distribution for the entire series awards the female the highest incidence, twenty compared to fourteen males.

Distributed among the chromate reactions were four patients who also reacted to gold chloride; one patient reacted to nickel and silver; four patients to nickel; one patient to nickel, copper and mercury; one patient to nickel, gold, silver, copper and zinc; one patient to nickel, mercury and cobalt; and one patient to mercury, leaving twenty-two single reactions. The positive test to nickel (1 per cent) in 243 patients reached an incidence of 10 per cent. Interpreting the positive test was not difficult because they all showed roughly the same degree. An urticarial response was characteristic on removing the patch with resolution of the reaction into a patch of subacute, papular dermatitis. Skog and Thyresson[11] using 5 per cent nickel sulfate found an incidence of 8.8 per cent in 8,005 patients.

SOURCES OF CHROMATE DERMATITIS

Skog and Thyresson[11] testing with 0.5 per cent found an incidence of 10.4 per cent chromate sensitivity in 8,005 patients. Becker[1] listed the causes of allergic contact dermatitis occurring in a group of government printers during July, 1951 to July, 1952, and found chromate sensitivity more common than rhus dermatitis, twenty-four cases compared to twenty-two, respectively. The concentration of the test solution was not stated. The author found thirty-four cases of chromate dermatitis in one year among private patients. This is a common etiology of contact dermatitis with an incidence for 1954 of 14 per cent. A thought comes up as to how much higher it should go before it becomes serious. Samitz[8] presents a chart of the hazards of the chromium industry, and in a table lists fifty-three classes of workers who may be exposed to chromate. Pirila and Kilpio[7] mention that Burkhardt noted that in alkali eczema some of the

cases represent an allergy to bichromate. These authors cited Bonnevie who found among twenty-nine males sensitized to bichromate, nine cases of dermatitis caused by chrome-tanned leather gloves. Among these nine men were four masons and three cement workers. Chrome leather which is commonly used in manufacturing gloves and shoes contains 5 per cent chromium compounds calculated as chrome trioxide (Cr_2O_3). When chrome leather comes in contact with alkaline cement or lime, the alkali forms soluble chromium compounds. Abundant sweating has apparently a similar effect. Grota[5] examined portions of leather that had become hard and brittle after a few weeks of wear. Microscopic study suggested the absence of tanning material in and around the collagen fibers. Chemical analysis revealed that the damaged leather contained fifteen times as much salt as the undamaged samples. This was due to the fact that chromium sulfate tanning material was chemically oxidized by perspiration to a water soluble chromium compound. Observing negative results from patch testing with chrome-tanned leather in chromate sensitive patients has been usual, but maybe something has been overlooked and chrome tanning and mordanting contribute in some unknown way to the incidence of chromate sensitivity.[4] Denton, Keenan and Birmingham[2] tested seven samples of cement for chromium content. Hexavalent chromium (Cr^6) values in the first filtrates varied from 0.03 to 6.9 micrograms per gram of cement powder. A patient with strong sensitivity to chromate was patch tested with 0.005 potassium dichromate and the first filtrates from cement samples 3, 4 and 7. Positive tests resulted. The authors believe that chromium in cement may initiate and maintain a cement dermatitis. Cement artisans are exposed to higher chromium levels because as moisture evaporates from cement slurries in contact with the skin, the percentage of hexavalent chromium rises.

COMMENTS

1. If chromate solutions are allowed to wet clothing, and especially if evaporation is prevented, the resulting circumstances favor the onset of sensitization aided, of course, by rubbing friction, pressure and maceration. Exacerbations of a healed chromate dermatitis would certainly occur from merely wetting the skin with a dilution of 0.1 per cent, and the chronicity would be maintained by dilutions of 0.01 per cent or probably much higher.

2. Patch tests do not affect the number of positive tests to aqueous chromates, based upon a large group of cases, but the concentration of the testing solutions remarkably influences the degree of positive reactions.

3. Testing for metal sensitivity in the presence of an extensive dermatitis may produce positive tests of no diagnostic significance. If tests are done, and the reactions persist several weeks, this indicates a degree of sensitivity of etiologic importance.

4. Concentrations of aqueous potassium chromate varying from 0.1 to 1 per cent may be used for patch tests. A concentration widely used is 0.5 per cent (1:200) by conventional patch test.

5. (a) *One or Two Plus Patch Test Reactions.*—Where this type of positivity stands in any scale of chromate sensitivity is difficult to state. The erythema, for example, bore no resemblance to the erythema from patch tests to 0.1 per cent in Table I, nor did it resemble the erythema from contact tests. Moreover, usually the symptoms and healing time bore no similarity. The reactions disappeared in three to four days. It was felt that these patients stood in the doorway of a chromate sensitivity. A little more contact, slight as it may be, might finally push them over into a true sensitivity. Another point that must be considered is that their one plus reaction indicates the same degree of sensitivity in them, host response, as a four plus reaction does in another patient. Clinical evidence exists that one plus chromate reaction indicates sensitivity because avoidance of contact with chrome plate produces a prompt improvement of the dermatitis. It is also possible that the state of the chromate valence and/or solubility might favor induction of one plus patch tests.

(b) *Four Plus Reactions.*—These responses highlighted typical sensitivity. Where the paper squares touched the skin, an embossed reaction developed—a brilliant erythema with massing of vesicles and even pustules. Flaring from the center, 3, 6 or even 9 centimeters was common. It was not necessary to ask to see the site of the tests. The patients pointed to them making it known how they itched. The healing time was reminiscent of chromate dermatitis, two or three weeks, a month or sometimes longer. Occasionally, a four plus reaction to 1 per cent chromate is associated with four plus reactions to all the metal salts tested. These cases may be instances of polyvalent sensitivity, but testing them with higher dilutions, 0.1 per cent, might readily eliminate some if not all the reactions except the true sensitizer.

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NEW MEDICAL PUBLICATIONS

In January, 1955, the *Journal of Chronic Diseases,* published by the C. V. Mosby Company, St. Louis, Missouri, made its appearance. This publication is to be devoted to the problems of chronic illness of all age groups. The first issue contained papers on "Determination of Prognosis in Chronic Disease, Illustrated by Systemic Lupus Erythematosus," "Hypertensive Vascular Disease: Description and Natural History," "The Results of Medical Treatment of Peptic Ulcer," "Care of the Long-Term Patient," "Influence of Sex and Sex Hormones upon the Development of Atherosclerosis and upon the Lipoproteins of Plasma," "The Changing Role of Chronic Disease," "Some Observations on the Beginnings of Chronic Disease," "Lung Cancer," and "On Muscular Cramps." Now that communicable diseases have in many instances been conquered, long-term illness has become one of the nation's major health problems. Publication of this journal is therefore timely.

Another new publication which made its initial appearance on the same date is *The Central African Journal of Medicine.* This bi-monthly journal, which is devoted to the medical problems of Rhodesia and Nyasaland, is an attractive publication, well printed on good paper. The initial number contained an article on David Livingston, to whose memory the journal is dedicated, as well as papers on "Some Aspects of Obstetrics in the African," "A Brief Survey of the Orthopaedic Aspects of Brucellosis in Central Africa," "Tuberculin Test Comparison Between the Heaf Multiple Puncture Apparatus and the Mantoux Test," "Njovera," "Artificial Radioactive Isotopes; Their Constitution and Use in Medicine," and "The Fevers of Africa. I. Bilharzial Fever." The publishers are to be congratulated on this venture.

OSTEOPOROSIS AND COMPRESSION FRACTURES FROM PROLONGED CORTISONE AND CORTICOTROPIN THERAPY

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THE early reversible side effects of cortisone and corticotropin therapy are familiar to all. They include acne, hirsutism, muscular weakness, psychic changes, hypertension, redistribution of fat deposits, moon facies, deeply pigmented skin, symptomatic metabolic alkalosis, sodium and water retention, potassium depletion, hyperglycemia, and impaired carbohydrate metabolism.

In addition, the following more serious complications have occurred: decreased resistance to infection, activation or reactivation of peptic ulcers, activation of unsuspected latent tuberculosis, psychosis, and collapse in stress situations (e.g.: fatal adrenal insufficiency following surgical procedures).

Osteoporosis with resultant vertebral compression fractures, a clinical feature of Cushing's syndrome, is not a common complication of cortisone and corticotropin therapy. In all probability, intensive and prolonged use of these hormones is a prerequisite. These osteopathic changes have a predilection for the lower dorsal and lumbar spine, and pelvic bones.

Bohland and Headley,[3] in September, 1950, were the first to report osseous complications following cortisone or corticotropin therapy. Osteoporosis and spontaneous fractures occurred in two elderly patients with rheumatoid arthritis. In June, 1952, Demartini, Grokoest, and Ragan[6] reported a series of five patients with rheumatoid arthritis, all of whom developed osteoporosis and compression fractures of the lower dorsal and lumbar spine following two to twenty months of hormone therapy. These patients were female, four of them postmenopausal, with moderately advanced rheumatoid arthritis and limited physical activity, all factors predisposing to osteoporosis. However, these authors concluded that the compression fractures were the result of intensive, protracted hormone therapy.

Soffer and Bader,[11] in July, 1952, described fractures in a fifty-eight-year-old female with lupus erythematosus disseminata receiving steroid therapy. In September, 1952, Teicher and Nelson[12] reported the same bony complications in a forty-eight-year-old male with pemphigus vulgaris. The osteoporosis was first noted after twenty-two months of continuous hormone therapy, and the compression fractures were noted eight

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months later. Four cases with similar changes were reviewed in June, 1953, in *Presse Méd.* by de Seze, Hubalt, and Renier.[7] At Massachusetts General Hospital[4] osteoporosis and compression fractures were demonstrated in a forty-three-year-old female with pemphigus vulgaris who had

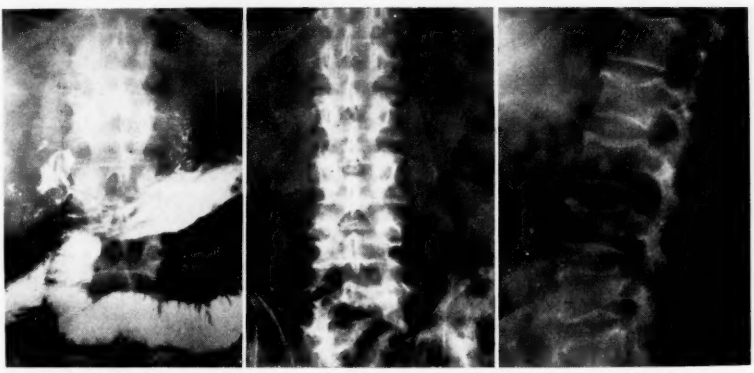

Fig. 1. (a) August 1952, negative for osteoporosis and compression fractures. (b and c) March 1954, with osteopathic changes.

Cushing's syndrome due to ACTH therapy. At autopsy, calcium deposits in both the tubular and the interstitial tissue of the kidneys were found. Vertebral compression fractures were reported by Curtiss et al[5] in four patients (including a nine-year-old boy) on steroid medication for rheumatoid arthritis. The only article we found reporting this complication in a patient with bronchial asthma was that of Irwin and his co-workers[8] in May, 1954.

During the past year we have noted two instances in which this complication occurred in asthmatic patients receiving prolonged steroid therapy.

CASE REPORTS

Case 1.—J. M., a white male, age fifty-seven, was first seen in November, 1946, for progressively severe intractable bronchial asthma of ten years' duration. Intradermal allergy testing at that time did not demonstrate positive skin tests. He was observed irregularly during the next five years. In June, 1951, the patient was hospitalized in severe status asthmaticus complicated by cardiac decompensation. In July, 1951, oral cortisone was given, the maintenance dose varying from 50 to 100 mg per day. In October, 1951, cortisone was stopped and corticotropin was substituted. The daily maintenance dose ranged from 20 to 40 mg of ACTH gel. In the next three and one-half years he had alternate remissions and exacerbations of the bronchial asthma, requiring thirteen hospitalizations for a total of two hundred sixteen days. During the hospitalization periods, his daily corticotropin dosage varied from 80 to 120 mg. In August, 1952, the patient began to note abdominal distress. At that time a duodenal ulcer was visualized on x-ray examination. In March, 1954, he complained of severe pain in the lower lumbar region. X-rays revealed marked osteoporosis of the lower dorsal and lumbar vertebrae and pelvis, with multiple compression fractures of the lumbar vertebrae (Fig. 1). X-ray of the spine in August, 1952, had shown none of these changes.

The following data of significance were noted in March, 1954: serum calcium 9.3 mg per 100 cc, serum phosphorous 3.4 mg per 100 cc. Total serum proteins 6 gm per 100 cc: serum albumin, 3.6 gm per 100 cc, and serum globulin 2.4 gm per 100 cc. CO_2 combining power 39.5 mEq per liter; chlorides 87.5 mEq per liter; alkaline phosphatase 6 Bodansky units; sodium 146 mEq per liter; potassium 5.2 mEq per liter; twenty-four hour urinary calcium excretion 194 mg; fasting blood sugar 206 mg per 100 cc; glucose tolerance curve showed decreased carbohydrate tolerance: 299 mg per 100 cc at one-half hour, 304 mg per 100 cc at one hour, 550 mg per 100 cc at two hours, and 370 mg per 100 cc at three hours.

In April, 1954, the patient was placed on combined estrogen and androgen therapy: .04 mg ethinyl estradiol and 10 mg methyltestosterone daily. After three weeks he noted definite relief of his back pain. Thereafter, he continued to take a daily maintenance dose, allowing a rest period of one week every four weeks, with no recurrence of the back pain. Subsequent x-rays have not shown objective evidence of decrease in the osteoporosis.

Case 2.—R. B., a white male, age forty-seven, was first seen in September, 1946, for allergy study. He had been entirely free of allergic symptoms until the late summer of 1930, when he developed seasonal hay fever. The initial episode of asthma occurred during the 1935 ragweed season. Subsequently, his asthma remained seasonal and desensitization pollen therapy provided relatively good control. In 1942, he entered the Army and was discharged in January, 1946. While stationed in Europe in 1944 and 1945, his asthma became increasingly severe and remained so on his return to the continental United States.

On initial examination, marked bilateral nasal polyposis was found in addition to bronchial asthma. Allergy testing by the intradermal method produced good whealing reactions. Positive skin tests were found to sage, ragweed, dust, cat ep., dog ep., wool, nuts, corn, shrimp, lobster, and crab. A diagnosis of seasonal hayfever (fall type), perennial allergic rhinitis with recurrent nasal polyposis, and bronchial asthma was made. Patient was placed on a desensitization regime, including the fall pollens and household dust, along with rigid dietary controls. It was soon evident that his symptoms were difficult to control. The bronchial asthma became progressively worse and his nose was rarely free of nasal polyps. From July, 1946, to June, 1951, when maintenance cortisone was first started, he had eighteen polypectomies. Repeated upper respiratory tract infections were the rule, and severe asthmatic episodes could be precipitated by direct exposure to cold air or the drinking of cold liquids. Ingestion of aspirin produced violent attacks of asthma. Continued desensitization therapy and the usual symptomatic medication failed to control his asthma or prevent recurrent polyposis.

In August, 1950, the patient was first placed on ACTH, with a good remission. Attempts at interruption of this therapy produced exacerbations of the bronchial asthma. In June, 1951, maintenance cortisone therapy was begun and has been continued to this date, on a daily maintenance dosage varying from 50 to 75 mg. With this therapy his bronchial asthma has been under adequate control and he is able to be gainfully employed. He has had but four nasal polypectomies, and none since October, 1953.

In November, 1954, x-rays of the spine showed early osteoporotic changes (Fig. 2). The following significant laboratory data were obtained: serum calcium 9.9 mg per 100 cc, serum phosphorus 4.4 mg per 100 cc. Total serum proteins 6.5 gm per 100 cc, with serum albumin 4.2 gm per 100 cc and serum globulin 2.3 gm per 100 cc. CO_2 combining power 25.9 mEq per liter; chlorides 102.7 mEq per liter; sodium 136 mEq per liter; potassium 5 mEq per liter; fasting blood sugar 74 mg per 100 cc. Urine calcium studies revealed 474 mg excreted per twenty-four hours.

The patient did not complain of back pain at this time. However, because of the enormous calcium loss, he was placed on testosterone therapy to prevent further deossification: 5 mg methyltestosterone daily, with a rest period of one week every four weeks.

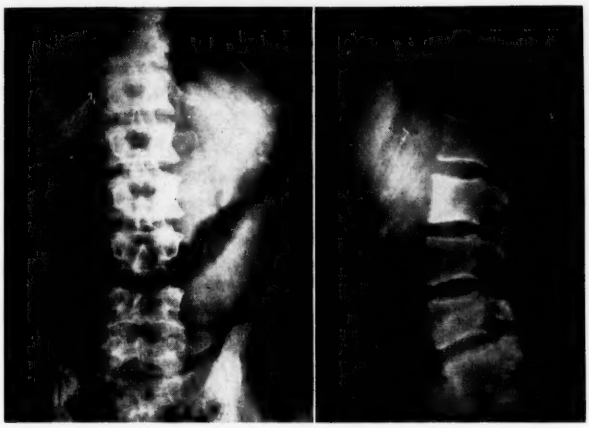

Fig. 2. Granular appearance of the vertebrae indicative of early osteoporosis.

DISCUSSION

In osteoporosis the primary anomaly is in bone matrix formation.[10] The difficulty, then, is a deficiency in protein metabolism, rather than in calcium and phosphorus metabolism. Several observations support this thesis: Becks et al[1] reported retardation of chondrogenesis and osteogenesis in normal rats on ACTH. Blunt et al[2] described similar findings in rabbits receiving cortisone, with resultant delayed healing of fractures.

In forty-three cases of Cushing's syndrome studied by Fuller Albright and his group,[8] osteoporosis was present in thirty-nine. Patients who have been on prolonged cortisone or corticotropin therapy may develop iatrogenic Cushing's disease. It is reasonable to expect that similar complications, including osteoporosis, will occur. Factors predisposing to osteoporosis in patients on steroid therapy are advanced age, menopause, and restricted activity. The added risk of this complication in such patients should be seriously considered before hormone therapy is given. Although only one instance of renal calculi has been observed, it is another potential danger related to negative calcium balance.

To insure the earliest possible detection of osteopathy secondary to steroid therapy, urinary calcium excretion studies should be performed serially; any determinations in excess of 150 mg per day point to a negative calcium balance. Similarly, serial x-ray studies provide early recognition of osteoporosis so that adequate treatment may be instituted before fractures occur.

Androgens and estrogens have been utilized in the treatment of all forms of osteoporosis. The studies of Reifenstein and Albright[9,10] in Cushing's disease have shown that estrogens favor a positive calcium balance, but testosterone compounds have a much more striking effect. Clinical observations following the use of these hormones have shown relief of pain, usually without x-ray evidence of decreased osteoporosis.

In addition to hormone therapy, a high protein diet should be given and activity encouraged. Calcium need not be added to the diet. Maintenance therapy should be interrupted every four to six weeks with a rest period of one week. The continued use of androgen in women may cause masculinizing effects. Because of the carcinogenic potentiality of androgen in men, the prostate gland must be examined periodically.

SUMMARY

1. Two cases of osteoporosis due to prolonged cortisone and corticotropin therapy have been presented.

2. In one, osteoporosis progressed to produce vertebral compression fractures and clinical symptoms of back pain.

3. Periodic x-rays of the spine and urinary calcium excretion studies have been suggested to recognize calcium depletion early and prevent fractures.

4. The use of androgens and estrogens in treatment is discussed.

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PRESSOR DRUGS

IV. The Safety of Inhalational Therapy in Human Patients

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THE marked increase in use of sympathomimetic drugs[2,22,23,26] has directed attention to the efficiency as well as the safety of their administration by inhalation. Inhalation therapy has been used for topical pulmonary therapy, as well as for the relief of bronchospasms.[2,3,5,7,8,10-15,20-24,27] Effects following inhalation of therapeutic quantities of drugs may differ from the effects following other methods of administration. Apparently, Ephraim in 1910[8] published the first paper on the relief of symptoms of asthma following inhalational therapy with l-epinephrine solution. Subsequent workers confirmed and extended his findings.[2,5,10-13,15,21,22,24,27] There appears to be general agreement regarding the efficiency of inhalational therapy with sympathomimetics, especially epinephrine. Particles having a diameter between 0.5 and 2.5 microns penetrate into the bronchioles and alveoli to relieve spasm of the bronchial muscles as well as local edema, reflected by improvement in respiratory function and increase in vital capacity.

The reports of most investigators and clinicians have indicated no adverse side effects following inhalational therapy. A search of the literature on inhalation of epinephrine solutions revealed only two critical reports. Galgiani et al[9] commented in 1939 on the local and systemic effects following inhalation from an unidentified nebulizer of 1:100 l-epinephrine solutions containing 0.2 per cent sodium bisulfite; the pH and the tonicity are not reported. No changes in pulse rate or blood pressure developed after ten deep inspirations of this solution from this nebulizer by twelve asthmatic patients during attacks, or by four normal persons. Under these conditions 0.008 mg of l-epinephrine was delivered per compression, of which not more than 3 per cent reached the lungs; contrasted with this lack of systemic effects, threshold responses developed after intravenous administration of 1 gamma/kg. Inhalation by rabbits and cats produced no histologic changes over periods up to seventy-one days; exposure for 117 to 121 days produced some tracheitis and loss of cilia.

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The 1:100 l-epinephrine solutions used in these studies were purchased on the open market, and represented the output by three different manufacturers; bioassays confirmed the correctness of their labeled potency. The 2.25 per cent r-epinephrine solution used was Vaponefrin,® also purchased on the open market. Pharmacodynamically, these solutions are similar; by the USP pressor method of bioassay,[28] their potencies were substantially identical. The standard Vaponefrin glass nebulizers used were obtained from the Vaponefrin Company, Upper Darby, Pennsylvania.

A patient with advanced pulmonary tuberculosis received inhalations every two hours for forty-eight hours before death; reddening of the trachea, leukocytic infiltration and some loss of epithelium were noted at autopsy.

Benson and Perlman[4] obtained 115 replies to a questionnaire in 1942, indicating decreasing relief of dyspnea, weakness, palpitation, nervousness and gastric distress after intratracheal administration of aerosolized l-epinephrine. Of 2,236 cases of asthma in their private practices, 648 used l-epinephrine from nebulizers; forty-eight died and autopsies were obtained on only ten. The identity, concentration, preservatives, pH, tonicity, frequency and duration of use of the solutions, and the characteristics of the atomizers or nebulizers used by these patients were not reported. Excessive and prolonged inhalation was stated to produce persistent cough, cyanosis, gastric distress with nausea and vomiting, sleeplessness, nervousness and tachycardia. Bronchoscopic examination revealed congestion of the trachea and primary bronchi. Chest x-rays revealed pneumonitis or atelectasis. These effects appear to be associated with the asthmatic condition rather than with the treatment, since they have been observed in many asthmatics who have not received inhalational therapy.[6,16,25,27,29]

Reports by a large number of investigators have failed to reveal any evidence of lack of safety following inhalational therapy over substantial periods of time.[2,3,5,12] Baldwin, Cournand and Richards[1] stated that several patients used Vaponefrin® for years without harm. Autopsies on two patients who had used it continuously for four years and for nine years failed to reveal any pathology of the bronchial mucosa. They concluded: "the daily inhalation of a bronchodilator must be considered harmless." Bullen[6] conducted autopsies on 132 hospitalized athmatic patients. In about one-third of this group he recorded the cause of death as asthma. There was no serious hazard to the heart, unless accompanied by emphysema. He concluded: "The long-continued use of epinephrine by injection and by inhalation produced no recognizable pathological changes in these patients." Larsen and Nielsen[14] observed no deleterious effects in their studies, in which 400 attacks of asthma in forty patients were relieved by the inhalation of 10 per cent (!) solutions of l-epinephrine.

Previous reports in this series[17,18,19] dealt with the chemistry, pharmacology, and safety of inhalation of enormous doses of 2.25 per cent r-epinephrine by rabbits, cats, dogs and monkeys. This report deals with a clinical, therapeutic study to determine the nature of any side effects which might develop following the inhalation of very large doses of l-epinephrine and of r-epinephrine in patients in whom such effects might be anticipated. Studies using both drugs were made on a total of 102 patients, which include thirty-one with hypertension; twenty-six with rheumatic disease; twenty-eight with cardiac disturbances due to arterial

TABLE I. AVERAGE CHANGES FOLLOWING INHALATION OF 48 COMPRESSIONS OF r—EPINEPHRINE AND l—EPINEPHRINE SOLUTIONS

	31 Hypertensives		26 Rheumatic Hearts		28 Cardiac Disturbances		16 Diabetics	
	r—	l—	r—	l—	r—	l—	r—	l—
Pulse Rate—beats/min.	—1.3	—0.8	—2.5	0.8	—0.4	—0.9	—	—
Systolic Pressure—mm Hg	—3.0	—3.8	—1.2	—1.8	—4.3	2.4	—	—
Diastolic Pressure—mm Hg	—2.1	—2.5	—0.4	—0.3	—2.8	0.5	—	—
Blood Sugar—mg %	—	—	—	—	—	—	0	—1.8

disease, and one with thyrotoxicosis. In addition, sixteen patients with diabetes were also tested for effects on blood sugar.

In studying these patients (except those with diabetes), the blood pressure and pulse rate were determined on each subject at rest in a chair, until three substantially identical values were obtained. A control 4-lead electrocardiogram was then taken. Since the usual therapeutic dose of epinephrine for the relief of bronchospastic conditions is four inhalations, and since we had found no subjective side effects from twelve consecutive inhalations, we adopted a "standard dose" of forty-eight consecutive inhalations in this study (in some patients ninety-six inhalations were administered with no different results than after forty-eight). This "standard dose" represents many times the customary or usual dose, and was felt to be adequate to develop any untoward effects. The blood pressure cuff and the electrodes were left in place during inhalation of the "standard dose"; at the conclusion of the last inhalation, the pulse rate, blood pressure and electrocardiogram were recorded. All patients were encouraged to report any symptoms which might develop. In the first test, either l-epinephrine or r-epinephrine was administered; after an interval of several weeks, each patient was similarly studied in a "cross-over test" with the other product. Each patient was seen at regular (usually weekly) intervals.

PATIENTS WITH HYPERTENSION

A group of thirty-one ambulatory patients were studied, each having a history of hypertension dating back at least five years; eleven males varied in age between thirty-eight and seventy-seven years, and twenty females between forty-one and seventy-two years. The original systolic blood pressures ranged from 156 to 252, averaging 198 mm Hg; diastolic pressures from 50 to 160, averaging 115 mm Hg. At the end of the inhalation period an occasional patient coughed, attributing this to a feeling of dryness of the throat. None of the patients complained of precordial pain, palpitation or nervousness during or after the experimental period. During the deep-breathing phase of the study, an occasional patient experienced vertigo which disappeared sponstaneously.

As shown in Table I, after inhalation of r-epinephrine, the average pulse rate decreased 1.3 beats per minute (increase of six to decrease of

twelve in various patients); after l-epinephrine, decrease of 0.8 beats (range from increase of six to decrease of six beats per minute). The maximal changes following inhalation of one product developed in a different patient than the maximal changes following the other. It was not felt that the differences in individual patients or in the average values had any significance.

Similarly, the systolic blood pressure after r-epinephrine decreased 3.0 mm Hg (increase 10 to decrease of 15 mm); after l-epinephrine decreased 3.8 mm (increase 40 to decrease 40 mm in range). The diastolic blood pressures decreased 2.1 mm (range from increase of 4 to decrease of 20 mm) and decrease of 2.5 mm (range from increase of 20 to decrease of 16 mm), respectively. In every instance, the blood pressures returned to the pre-inhalation levels within five minutes. The slight to moderate decreases in systolic pressures might be attributed to overbreathing.

Of this group, sixteen demonstrated abnormal electrocardiograms, varying from left ventricular preponderance and strain to bundle branch block and delayed A-V conduction. Several exhibited chronic coronary insufficiency, others left axis deviation. Comparison of the control electrocardiograms in all four leads with those obtained after inhalation of either r-epinephrine or l-epinephrine, showed no changes in the P-R, the Q-T, or the QRS values; all complexes remained at the control level, and exhibited no significant alterations in time or contour.

Considering the lack of effect on the pulse rate, the blood pressures, and the electrocardiogram, it is concluded that these patients showed no contraindication to the inhalational use of l-epinephrine or of r-epinephrine from this nebulizer.

PATIENTS WITH RHEUMATIC HEART DISEASE

A group of twenty females and six males, ranging in age from eight to fifty-nine years, were considered as having "rheumatic heart disease" on the basis of the usual diagnostic criteria. Their pre-treatment blood pressures ranged from 80 to 150 and from 0 to 100 mm, averaging 124/64 mm. Of the group, eight showed evidence of mitral stenosis, ten had double mitral lesions, and four mitral and aortic lesions. Auricular fibrillation was present in eight, and two were in cardiac congestive failure. Three had aortic insufficiency and one showed aortic stenosis.

After administration of the "standard dose" of r-epinephrine and of l-epinephrine, the pulse changes showed an average decrease of 2.5 (increase of 12 to decrease of 12) and an average increase of 0.8 (range from increase of six to decrease of twelve) beats per minute following each product. The systolic blood pressures showed average decreases of 1.2 mm (range from increase of 10 to decrease of 14) and of 1.8 mm (range from increase of 6 to decrease of 36 mm); the diastolic pressures showed average decreases of 0.4 mm (from increase of 8 to decrease of 12

mm) and of 0.3 mm (range from increase of 8 to decrease of 14 mm) respectively.

The control electrocardiograms revealed eight cases of auricular fibrillation, one of premature auricular and ventricular complexes, one case of right bundle branch block and three cases demonstrated T-wave changes. Evidence of auricular strain was observed in seven patients. Electrocardiograms were within normal limits in eight patients of the group. No differences in time or contour could be detected in comparing electrocardiograms taken after inhalation with those taken before treatment. No symptoms developed in any of the members of this group during or following these inhalations.

The inhalation of r-epinephrine or of l-epinephrine by these patients with rheumatic valvular heart disease and a history of precordial pain failed to produce any significant changes in pulse rate, in blood pressures or in electrocardiogram. No contraindications developed.

PATIENTS WITH CARDIAC DISTURBANCES DUE TO ARTERIAL DISEASE

This group of twenty-eight ambulatory patients between forty-one and seventy-three years old each showed precordial pain due to organic coronary insufficiency. The injection of epinephrine to such patients is contraindicated, even though such patients have no particular immunity to bronchial asthma. Therefore, we were interested in determining whether inhalational therapy to relieve their asthmatic attacks is to be denied them, or whether it may be safely used. In addition to electrocardiographic evidence of coronary insufficiency, 9 showed previous myocardial infarction, and 2 luetic cardiovascular disease with aortic aneurysm.

One member of the group was given the "standard dose" of air as a control on the entire series; the pulse rate dropped six beats per minute; the systolic blood pressure decreased 2 mm and the diastolic pressure dropped 8 mm. After administration of the "standard dose" of r-epinephrine and of l-epinephrine to the patients in this entire group, the pulse changes showed average decreases of 0.4 beats (range increases of 6 to decrease of 12) per minute, and of 0.9 beats (increase of ten to decrease of eight) per minute, respectively. The systolic blood pressures showed an average decrease of 4.3 mm (range from increase of 2 to decrease of 20 mm), and an average increase of 2.4 mm (range from increase of 56 mm to decrease of 12 mm); the diastolic pressures showed an average decrease of 2.8 mm (range from increase of 6 to decrease of 20 mm) and an average increase of 0.5 mm (range from increase of 14 to decrease of 6 mm) respectively.

There were no changes whatever in time or contour of the electrocardiograms; none of the group complained of precordial or of substernal pain following inhalation; there were no increases in premature ventricular complexes nor in ectopic complexes in any patient.

Since these inhalations did not produce changes in pulse rate, blood

pressure or electrocardiograms, and did not produce pain, cardiac disturbances due to arterial disease are not a contraindication to inhalational therapy for the treatment of bronchial asthma.

PATIENT WITH THYROTOXICOSIS

The injection of l-epinephrine or related sympathomimetics, is contraindicated to thyrotoxicotic patients; in fact, this has been used as one means of diagnosis. Since no untoward systemic effects followed inhalation by patients with cardiac disturbances due to arterial disease, a test was made with the "standard dose" of r-epinephrine on one patient in this classification. R. S., white woman, aged sixty-five, had precordial pain and dyspnea on exertion; peripheral blood vessels were soft, pulse of the high-tension type, and sitting or lying blood pressures 240/120 mm. The electrocardiogram revealed left ventricular preponderance; chest x-rays showed cardiac enlargement with left ventricular hypertrophy; fluoroscopy revealed an aneurysm of the thoracic aorta. The basal metabolic rate ranged between plus 62 per cent and plus 71 per cent. After being in bed all day the pulse rate was 72, and the blood pressure 240/86. After administering the "standard dose" of r-epinephrine, the pulse rate increased to 76 beats per minute and the blood pressure was 230/90 mm. No untoward manifestations whatever developed following inhalation and there were no changes in the electrocardiogram. This single case is not sufficient for a broad opinion, but does appear to justify cautious inhalation of a therapeutic dose of r-epinephrine, since this patient received many times the therapeutic dose at a single sitting without apparent deleterious effect.

PATIENTS WITH DIABETES

This group consisted of sixteen patients with uncontrolled diabetes, not receiving insulin, and varying in age from thirty-nine to seventy-two years. Since injection of l-epinephrine produces a rise in blood sugar, it has been contraindicated in diabetes mellitus. Therefore we were interested in determining the safety of administration of r-epinephrine and l-epinephrine by inhalation to such patients.

Considering the rapidity of relief of bronchial asthma after inhalation, it was believed that ten minutes would be a suitable time interval to measure any changes in blood sugar levels following inhalation of a "standard dose". This group were bled just before, and ten minutes after, inhalation of r-epinephrine; after several weeks the patients were "crossed over," receiving the "standard dose" of l-epinephrine. Following r-epinephrine the average change in blood sugar was 0 per cent (range from increase of 5 to decrease of 6 per cent); following l-epinephrine, the average change was a decrease of 1.8 per cent (range from increase of 4 to decrease of 15 per cent). These deviations fall within the limits of ex-

perimental error, indicating in this acute study that there was no significant change in blood sugar levels as the result of the inhalation of the "standard dose."

SUMMARY

Studies have been made on eighty-six patients with various types of cardiac involvement, and on sixteen patients with uncontrolled diabetes, to determine the possible development of untoward effects following the inhalation of 2.25 per cent r-epinephrine solution (Vaponefrin®) or of 1:100 l-epinephrine solution. All inhalations were produced in a commercial glass Vaponefrin nebulizer with a hand bulb; different results might have followed use of a different type of nebulizer. Although the usual treatment for bronchial asthma is the administration of material produced by four inhalations, we wished to give a larger quantity in this study so we established a "standard dose" of forty-eight inhalations. (In some tests, administration of ninety-six inhalations produced the same responses as those following forty-eight inhalations). The pulse rates, blood pressures and 4-lead electrocardiograms were determined on the cardiac patients, and blood sugar levels were determined on those with diabetes, immediately before and from time to time after inhalation. Each patient received the "standard dose" of one form of epinephrine and after a suitable interval received the other form, as a "cross over."

In addition, the "standard dose" of r-epinephrine was administered to a patient with thyrotoxicosis, to determine the possible development of untoward effects. Having in mind the statements in the literature regarding possible development of various side effects, efforts were made to observe each patient for such possible responses; each patient was requested to report the development of any untoward effects following inhalation.

Our findings confirm those of previous investigators, that no untoward effects developed following inhalation of many times the therapeutic dose of r-epinephrine or of l-epinephrine under our conditions of study, in these patients having a history of hypertension, of precordial pain and rheumatic heart disease, of cardiac disturbances due to arterial disease and pain due to organic coronary insufficiency, in a case of toxic adenoma of the thyroid, or in uncontrolled diabetics. None of this group showed significant changes in pulse rate, in systolic or diastolic blood pressure, in electrocardiographic timing and contour, or in blood sugar level.

CONCLUSION

In patients with bronchial asthma or bronchospasms, the simultaneous presence of hypertension, rheumatic heart disease, cardiac disturbance due to arterial disease, or diabetes, is not a contraindication to the use of r-epinephrine or l-epinephrine solution by inhalation.

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POLIOMYELITIS AND THE ALLERGIC CONSTITUTION

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A MOST perplexing peculiarity of poliomyelitis, in comparison to other communicable diseases with known microbial causative organisms, is its unique incidence. Some of the features of this peculiarity are: (1) an unpredictable and extremely variable contagiosity in any one locus where an outbreak occurs; (2) a bizarre symptomatology which results occasionally in diagnostic confusion, due to a great variety of types or degrees of manifestations resulting from a poliomyelitis infection of the organism, and which may entitle poliomyelitis to be called an "imitator" of other diseases, somewhat like allergic diseases today and syphilis when it was more prevalent; (3) a puzzling epidemiology despite much research and an apparently known causative viral agent or group of viral agents; (4) a pronounced seasonal increased incidence of the disease, which seems to bear some relationship to respiratory infections during the summer at the very time of the year when respiratory infections are least frequent; (5) an outstanding and frequent history of recent inadequate rest or marked overwork preceding the onset of poliomyelitis; (6) evidence of some immunologic activity in the body which appears to intensify or lessen the barriers to infection resulting from a poliomyelitis virus, i.e., pertussis vaccinations, et cetera, in some poliomyelitis cases;[2] and (7) an increased incidence in recent years of poliomyelitis, which appears to be coincident with an apparent simultaneous rise in the prevalence of allergic diseases, as well as phenomenal increase in the development and use of the so-called "miracle drugs" (antibiotics, antihistamines, cortisone and other similar drugs).

The aforementioned facts have in many respects contributed to the "fear of the unknown" factor and have caused panic among the laity. The fact is that severe poliomyelitis is statistically rare, even during an epidemic; however, poliomyelitis and its prevention are important and, because of the nature of this disease, and the care which a severe case requires, the disease deserves all the consideration it is accorded.

Aycock[1] has presented evidence for and considers the constitution of the individual who develops poliomyelitis as an etiologically significant problem.

The nasopharynx appears to have been rather well established in recent evidence[3,6] as a *locus minoris resistentiae* for infection by the viral agents responsible for the development of severe poliomyelitis, such as the bulbar type. Operations like tonsillectomies or adenoidectomies have been proved by many studies to influence markedly the course of a poliomyelitis infection.[3] The nasopharynx is also the seat of most of the obvious pathology in the vast majority of patients who suffer from allergic disorders. The

allergic constitution seems to manifest a marked preference for the same season of the year as poliomyelitis infections, namely, the summer. It appears that there are many points of similarity between the allergic constitution and a constitution type predisposed to poliomyelitis, a hypothetical polioergic constitution, such as lowered resistance to infection in general (perhaps especially relating to the nasopharynx) and the etiologic significance of inadequate rest. Therefore, a "polioergic constitution" or diathesis was conceived as a possible explanation for some of the baffling aspects of poliomyelitis. Hence, this concept was subjected to a statistical study of the incidence of allergy in poliomyelitis patients. For this purpose the poliomyelitis epidemics of 1949 and 1950 presented an excellent opportunity.[4]

Two studies were made, one in 1949 and the other in 1950, on a total of 300 poliomyelitis cases. In carrying out these studies every effort was made to prevent the influence of any personal bias on the results, and the results were submitted for comment and criticism to experts on poliomyelitis, allergy, and statistics. Every effort was made also to avoid creating a "phobia of poliomyelitis" among the large numbers of people who are afflicted with an allergic disease. Only the major allergic conditions, such as bronchial asthma, allergic rhinitis, urticaria, and eczema, were included in this investigation. Other minor allergic manifestations were purposely excluded in order to avoid any doubts as to the allergic diagnosis.

The first study was carried out in 1949 among 205 poliomyelitis patients assigned to me at random, so that there could be no possible influence of the type of case, by the Bureau of Preventable Diseases of the New York City Health Department in which I was an epidemiologist at the time. These patients were analyzed with respect to an allergic diagnosis prior to any knowledge of the clinical aspect of the poliomyelitis infection. In every one of the 205 cases, the medical-hospital diagnosis of infection and the type of poliomyelitis was confirmed by the diagnostician of the New York City Health Department, Bureau of Preventable Diseases. Between June and November, 1949, each of the cases was investigated from the viewpoint of determining the existence of major allergic syndromes. It is well recognized by immunologists and allergists that an accurate history is the most important single criterion in the diagnosis of allergy.[5] An extensive, thorough history was obtained in each case. Every precaution was taken to avoid suggesting in any way that an allergic survey was being made and thus influencing the diagnosis. Questions were first asked in a casual fashion as to whether the patient "suffered from other illnesses, such as diabetes or kidney conditions." On the basis of the history, the 205 poliomyelitis cases were classified into two main groups: Group I—Allergic, and Group II—Nonallergic. Group I was subdivided into two groups, Group I-a, consisting of poliomyelitis patients who had a major allergic disorder, and Group I-b, composed of poliomyelitis patients with a family history of

TABLE I. INCIDENCE OF BULBAR POLIOMYELITIS AND MORTALITY IN ALLERGIC AND NONALLERGIC PERSONS—1949

	No. of Cases	Percent of Cases	No. Bulbar Cases	Percent of Bulbar Cases	No. of Deaths	Percent of Death
Allergy Group I-a	29	27	9	31	1	3
Allergy Group I-b	78	73	17	22	4	5
Total	107	100 (52% of total)	26	24	5	5
Nonallergy Group II	98	100 (48% of total)	10	10	1	1
Grand Total	205	100	36	18	6	3

these same major allergic conditions in close relatives (siblings, parents, grandparents, aunts and uncles). I wish to emphasize that the type, severity, or clinical course of the poliomyelitis was not known to me at the time of the allergic classification.

Table I gives the results obtained in my first study. As may be seen from this table, there were 107 cases (52 per cent) of poliomyelitis in the allergy group (twenty-nine, or 27 per cent, in Group I-a, and seventy-eight, or 73 per cent, in Group I-b), and ninety-eight cases (48 per cent) in the nonallergic group (Group II). Of greater interest, however, is the incidence of bulbar cases. There were twenty-six such cases (24 per cent) in the allergy group (nine, or 31 per cent, in Group I-a and seventeen, or 22 per cent, in Group I-b), as compared to ten cases (10 per cent) in the nonallergy group. Thus, the incidence of bulbar poliomyelitis was 2.4 times greater in the allergic than in the nonallergic group. It is interesting to note also that the incidence of bulbar poliomyelitis in allergic patients (Group I-a) was 31 per cent, as compared to the 22 per cent in patients with only a positive family history of allergy.

The total number of deaths in Group I was five, or 5 per cent of the total allergy patients, whereas in Group II there was only one death, or 1 per cent of the nonallergy patients, a mortality rate for Group I of five times that of Group II.

The degree of paralysis was not determined carefully enough to warrant reporting. However, there seemed to be more cases of paralytic poliomyelitis in Group I than in Group II. As shown in Table II, among the twenty-nine cases of poliomyelitis occurring in individuals with a major allergy (Group I-a), only eight nonparalytic cases occurred (27 per cent). On the other hand, of the ninety-eight nonallergic patients, Group II, there were forty nonparalytic cases, or 41 per cent. The average age of the patients comprising Group I was lower than that of those comprising Group II. Among the twenty-nine allergic individuals, only one patient was over the age of twenty, whereas among a list of twenty-nine cases selected at random from the nonallergic group there were five patients over the age of twenty.

TABLE II.
POLIOMYELITIS CASES IN PERSONS WITH MAJOR ALLERGIES (GROUP I-a)

Case	Age	Major Allergy	Bulbar	Paralytic	Nonparalytic
J.M.	9	Hay Fever		X	
R.L.	10	Asthma	X	X	
J.V.	9	Hay Fever		X	
K.R.	4½	Hay Fever	X	X	
J.G.	6	Hay Fever		X	
M.C.	9	Eczema			X
E.H.	2	Eczema			X
A.M.	11	Hay Fever	X	X	
R.S.	5½	Hay Fever	X	X	
R.P.	17	Hay Fever	X	X	
R.S.	9	Asthma		X	
R.B.	6	Asthma			X
W.C.	10	Asthma	X	X	
M.J.	9	Hay Fever		X	
A.G.	1½	Asthma		X	
S.L.	14½	Asthma (made exitus)	X	X	
A.C.	3	Urticaria		X	
D.S.	24	Hay Fever			X
P.G.	7	Asthma		X	
B.C.	12	Hay Fever		X	
J.C.	17	Hay Fever			X
A.S.	9 mo.	Urticaria		X	
A.S.	8½	Asthma			X
J.O.	5	Asthma			X
A.K.	6½	Asthma	X	X	
M.C.	18	Hay Fever	X	X	
M.M.	8	Asthma		X	
N.R.	4	Asthma		X	
M.C.	11	Hay Fever			X
Total No. of Cases 29			9	21	8

The data from Table I suggests that patients with an allergic constitution contracting poliomyelitis are more likely to develop bulbar poliomyelitis than those who are nonallergic.

In view of these findings, the study was continued during the poliomyelitis epidemic of 1950. Between June and November, 1950, ninety-five cases of poliomyelitis were studied in exactly the same way as those in 1949. The results of this study are given in Table III. Forty-five of the cases (47 per cent) of poliomyelitis were in the allergy group (seventeen, or 38 per cent, in Group I-a and twenty-eight, or 62 per cent, in Group I-b), and fifty (53 per cent) in the nonallergy group, Group II.

The total incidence of bulbar poliomyelitis in the allergy group was 29 per cent (thirteen cases), as compared to only 6 per cent (three cases) in the nonallergic group. In the allergy group the incidence of bulbar poliomyelitis in the patients with a major allergy (Group I-a) was 47 per cent, while the incidence in patients with only a positive family history of a major allergy (Group I-b) was 18 per cent.

The total number of deaths in Groups I-a and I-b was six, or 13 per cent of the total allergy groups, whereas in Group II there was only one death, or 2 per cent of the nonallergy group, a ratio of 6.5 to 1.

Table IV summarizes the data from the two studies comprising three hundred poliomyelitis cases. Of the total of 300 cases, 152 occurred in the allergy group (forty-six in Group I-a and 106 in Group I-b) and 148 in the nonallergy group. The incidence of bulbar poliomyelitis in the allergy

TABLE III. INCIDENCE OF BULBAR POLIOMYELITIS AND MORTALITY IN ALLERGIC AND NONALLERGIC PERSONS—1950

	No. of Cases	Percent of Cases	No. Bulbar Cases	Percent of Bulbar Cases	No. of Deaths	Percent of Death
Allergy Group I-a	17	38	8	47	3	18
Allergy Group I-b	28	62	5	18	3	11
Total	45	100 (47% of total)	13	29	6	13
Nonallergy Group II	50	100 (53% of total)	3	6	1	2
Grand Total	95	100	16	17	7	7

TABLE IV. INCIDENCE OF BULBAR POLIOMYELITIS AND MORTALITY IN ALLERGIC AND NONALLERGIC PERSONS—1949 & 1950
(Combined Data from Tables I and III)

	No. of Cases	No. Bulbar Cases	Percent of Bulbar Cases	No. of Deaths	Percent of Death
Allergy Group I-a	46	17	37	4	8
Allergy Group I-b	106	22	21	7	7
Total	152	39	29	11	7.5
Nonallergy Group II	148	13	9	2	1
Grand Total	300	52	17	13	4

group, however, was 29 per cent as compared to 9 per cent in the nonallergy group, a ratio of over three to one. The mortality in the allergy group was also greater (7.5 per cent) than in the nonallergy group (1 per cent).

COMMENT

In each of the two studies the number of poliomyelitis patients who proved to have a major allergic history was approximately equal to the number without such a history (107 compared to 98 in the first study, and forty-five as against fifty in the second). In each of the studies the incidence of bulbar poliomyelitis was greater in the group with a major allergic history than in the group without it (24 per cent compared to 10 per cent in the first study, and 29 per cent compared to 6 per cent in the second study). The mortality in the cases with a major allergic history was also greater than in those without such a history in each of the two studies (5 per cent as compared with 1 per cent in the first study, and 13 per cent as against 2 per cent in the second).

Thus, the results of the second study closely parallel those of the first study. These findings would seem to warrant a similar study on a large scale by allergists in various parts of the country in order to determine whether the allergic constitution is, as our results would seem to indicate, related to the severity of poliomyelitis.

SUMMARY

A study has been made of the incidence and severity of poliomyelitis in patients with an allergic history, and those without it in two poliomyelitis epidemics, 1949 and 1950. In both epidemics, the incidence of the disease was approximately the same in both groups. However, the incidence of bulbar cases was 2.4 times as great in the 1949 epidemic and five times as great in the 1950 epidemic in the group with allergic history than in the group without it. The mortality in each epidemic was also greater in each epidemic in the group with an allergic history than in the group without it.

Author's Note: The recently announced success of the Salk poliomyelitis vaccine in the phenomenal 1954 large scale tests which were carried out at great expense is a very good example of what an excellent "private enterprise" organization, such as the National Foundation for Infantile Paralysis, can accomplish efficiently and rapidly. In view of the present unavoidable situation, the results of the study presented in this article might be significant in making decisions on the priority for vaccination.

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THIRD ANNUAL SYMPOSIUM ON ANTIBIOTICS

The Third Annual Symposium on Antibiotics, sponsored by the Food and Drug Administration, Division of Antibiotics, U. S. Department of Health, Education, and Welfare, and the journals *Antibiotics and Chemotherapy* and *Antibiotic Medicine*, will be held in Washington, D. C., November 2-4, 1955.

Those desiring to participate should submit an abstract in triplicate of not more than 200 words before September 21, 1955, and the original manuscript with one copy by October 3, 1955 to Dr. Henry Welch, Director, Division of Antibiotics, Food and Drug Administration, U. S. Department of Health, Education, and Welfare, Washington 25, D. C. Manuscripts must contain new and unpublished material. Further details can be obtained from the office of Dr. Welch.

THE USE OF SONIC VIBRATIONS IN THE PREPARATION OF FUNGOUS EXTRACTS

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THE preparation of extracts of fungi for skin testing has been undertaken in many ways. Most of the commonly used procedures involve the production of mature mats of the fungus which may then be washed and extracted with normal saline or special extracting fluids. The mats may be ground in a mortar or ball mill prior to or during extraction or they may be allowed to steep in the extracting fluid for extended periods of time.

Prince and Morrow[18] studied many variations of old procedures and also investigated new methods including lyophilization and defatting of the mat prior to extraction. They found no significant difference between the extracts prepared by these varied methods. Prince et al[19] found that some of the active principle could be recovered from the water with which the mats of fungus were rinsed. They also found that dialysis resulted in the retention of most of the active principle within the dialyzing membrane. Their most active preparation, however, proved to be a filtrate of the broth upon which the fungus was grown. Acetone precipitated extracts prepared from filtrates of the medium (Prince et al[20]) proved to be somewhat more effective.

The search for other procedures in the preparation of fungus extracts has been dictated by the observation that many extracts are impotent but irritative, thereby giving an unwarranted number of falsely positive reactions. One of the primary objectives of these various investigations, however, has been to produce extracts which are more specific. It has become increasingly apparent in recent years that allergens contain many separate components. This multiple composition of allergens was convincingly demonstrated for pollen extracts by Becker and Munoz[1] who were able to show the presence of at least five separate components in ragweed extracts. It would therefore seem possible that the nonspecific reactions obtained with many extracts are due to the presence of allergenic components common to other allergens. It is also equally possible that the loss of specificity in many extracts is due to the destruction, during preparation, of one or more components which are responsible for the specific reaction of the extract.

The destruction of that portion of the allergen responsible for specificity may come about during the drying procedure used in many of the techniques, or it may be lost during the grinding process used by many workers. In order to avoid both drying and grinding procedures, mats of the fungus, suspended in the extracting medium, were exposed to sonic vibrations.

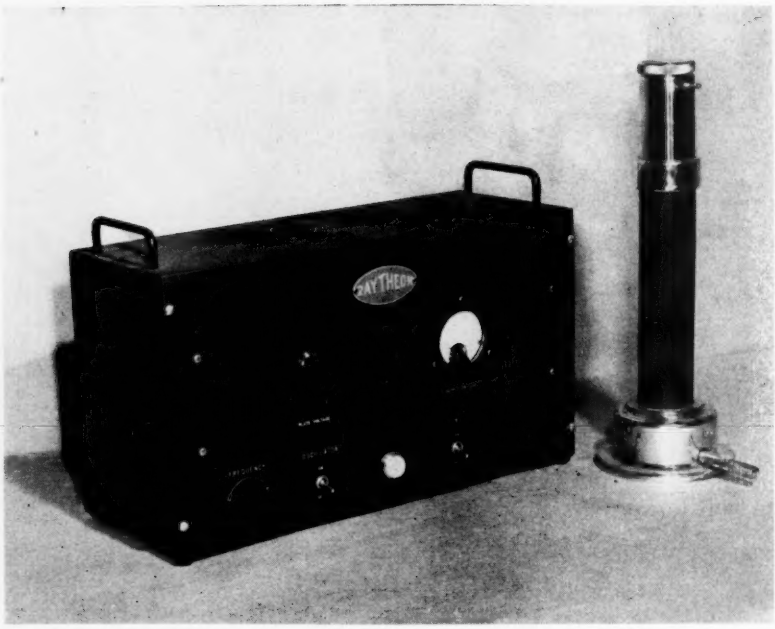

Fig. 1.

The action of sonic vibrations on biologic systems has received considerable attention from biologists in many fields. A sound having a frequency of more than 32,000 vibrations per second is generally inaudible to the human ear. However, a sharp line cannot be drawn between the audible and inaudible regions, and hence ultrasonics are usually considered to be any frequency above 16,000 cycles per second.

Chambers and Gains[4] studied the effect of audible sound waves of 8,900 cycles per second, but of high intensity, on several biologic systems. Among other materials, they found that suspensions of red blood cells were completely lysed after ten minutes' treatment. Since the action of sonic vibrations on micro-organisms is essentially that of a mill, it has been used by many investigators for the preparation of antigens, haptens, and enzyme preparations. Thus, Flosdorf, Kimball et al[7] used sonic vibrations of 8,900 cycles per second to rupture bacterial cells and liberate certain antigenic substances which are normally very labile. Pappenheimer and Hendee[15] used sonic vibrations of 9,000 cps to extract various enzymes from bacteria.

The action of sonic vibrations on molds has been shown to be the same as on bacteria by Kuster and Theismann.[12] Also, it has been shown by Van den Schrieck and Van Gordsenhoven[22] that ultrasonics at frequencies of 1,000 Kc on serum and hemolysins did not alter their sero-

logic activity. An excellent review of the action of ultrasonics on biological systems may be had by consulting Grabar.[8]

In view of the indications that sonic vibrations, at least in the range of 9,000 cps, have little or no denaturation effects on the chemical identity of the cell material of micro-organisms, extracts were prepared by this method and tested.

MATERIALS AND METHODS

Apparatus.—The apparatus used in this work was a laboratory model of a device, made by the Raytheon Manufacturing Company of Waltham, Massachusetts, for the application of intense sound energy to small quantities of liquid. This apparatus, shown in Figure 1, was generously loaned to me by Professor Kurt S. Lion of the Massachusetts Institute of Technology. It consists of a water-jacketed stainless steel cup, the bottom of which is a diaphragm that is vibrated by a laminated nickel structure connected to it. This "magnetostrictor transducer" is driven by an electronic power oscillator having an output of approximately 60 watts, at a frequency of about 9,000 cps. The entire cup assembly can be removed and sterilized in the autoclave.

Procedure.—The experimental fungi to be used for clinical testing were inoculated into 250 ml flasks containing 75 ml of the following medium:

Potassium phosphate (K_2HPO_4)	1.0 gm
Potassium chloride (KCl)	0.5 gm
Magnesium sulfate ($MgSO_4 \cdot 7H_2O$)	0.5 gm
Ferrous sulfate ($FeSO_4$)	0.01 gm
Glucose	10.0 gm
Asparagine	1.5 gm
Water	1,000. ml

The cultures were incubated at room temperature until mature, about twenty days. At this time the mats were harvested and suspended in normal saline in a weight-volume ratio of 1:20. These suspensions were then introduced into the transducer cup of the magnetostrictor and subjected to sonic vibrations of 9,000 cps for a period of thirty minutes. It was determined by microscopic examination that most cells were ruptured after this period of time.

The suspensions were then filtered through sintered glass filters of UF porosity and the sterility of the filtrates was made certain. Five per cent glycerine was then added to the extracts to be used for scratch testing of children. The glycerine served to keep the drop of extract applied to the skin of the patient from drying out too rapidly and from rolling off the backs of the more active children.

The extract used for comparison and designated as "standard extract" was purchased from a well-known supplier.

TABLE I. FUNGI USED IN SKIN TESTING

No.	Identification	Source of Isolation
1	Alternaria brassicicola (Schwein) wiltsh. (Syn. A. circinans)	*Cabbage
2	Alternaria tenuis auct.	*Callistephus Balls-dark rose
3	Alternaria tenuis auct.	*Carrot
4	Alternaria tenuis auct.	Pelargonium
5	Alternaria tenuis auct.	Schinus molle
6	Alternaria tenuis sensu stricto	From plates exposed at M.G.H.
7	Alternaria tenuis sensu stricto	From plates exposed at M.G.H.
8	Sporodesmium pluriseptatum (Karsten and Har. pro var.) Peck (Syn. Stemphylium ilicis)	*Cucumber
9	Stemphylium consortiale (Thum.) Groves and Skolka (Syn. S. ilicis)	*Primula
10	Stemphylium radicinum (M., D. and E.) Neerg.	*Carrot
11	Cladosporium sp.	From plates exposed at M.G.H.
12	Epicoccum sp.	From plates exposed at M.G.H.

M.G.H.—Massachusetts General Hospital.
*Single Spore Isolates.

Fungi Used in Testing.—A review of the literature indicates that the greatest number of positive reactions are obtained with extracts of the common airborne fungus, *Alternaria*. Thus, the following investigators have reported the per cent of positive reactions to *Alternaria* as indicated: Brown,[8] thirty; Lamson,[13] thirty-six; Pratt,[17] twenty-five; Chobot,[5] twenty-seven; Harsh and Allen,[10] eighteen. Feinberg,[6] Blumstein and McReynolds,[2] and Hampton and Lowe,[9] among others, report *Alternaria* as the principal reactor. In addition, a questionnaire circulated to members of the Society for the Study of Asthma and Allied Conditions revealed that, of forty-seven members answering, forty-four rated *Alternaria* as the most important fungus concerned with inhalant allergy in their practice.

In view of the position of importance of *Alternaria,* both in its ubiquity and its ability to elicit positive reactions, this organism was the major mold used in the present study.

In order to determine the possibility of species sensitivity to *Alternaria,* it was important to secure authentically identified species of this genus. Table I lists the fungi used in the preparation of extracts which were employed in the clinical work reported below.

Cultures 1 through 5 and 8 through 10 were generously supplied by Dr. Paul Neergaard of Copenhagen, one of the authorities on this difficult genus.[14] It is important to note that these cultures were isolated in Copenhagen. In spite of the insistence of many workers that local isolates must be used to secure good clinical reactions, these isolates proved to be very active, comparing favorably with local isolates. Cultures 8 to 10 belong to genera closely related to *Alternaria* and were included to determine the possibility of the elicitation of common reactions.

Cultures Nos. 6 and 7 are local isolates which were verified by Dr. Neergaard. Culture No. 11 was included as a representative of the genus *Cladosporium* and is a local isolate, probably *Cladosporium herbarum.* Culture No. 12 is an isolate of *Epicoccum,* a fungus which appeared repeatedly on plates exposed during a survey, which I conducted in 1952.[11]

TABLE II. READING OF SCRATCH SKIN TESTS

0	= reactions of same size as in controls
+	= reactions twice as large as in controls
+ +	= erythema 15-20 mm. in diameter
+ + +	= erythema 20-25 mm. in diameter
+ + + +	= erythema exceeding 25 mm. in diameter

Clinical Testing.—The clinical work on this problem was carried out at the Children's Hospital of Boston with the co-operation and encouragement of Dr. Lewis Webb Hill. The patients ranged in age from three and one-half to eleven years old. All patients reporting to the allergy clinic were routinely tested by the scratch method with the "standard extract," the experimental extracts listed in Table I, and with five per cent aqueous solution of glycerine as a control. In addition, each patient was tested with extracts of a standard series of allergens. These served as additional controls for the experimental series.

The reactions were read after twenty minutes and were recorded as one to four plus, according to their size. Table II lists the grading used in recording the reactions.

RESULTS

A total of seventy-five patients were tested with the experimental extracts. Of these, 25.3 per cent reacted to one or more of the experimental extracts. Forty-eight per cent of the patients did not react to the experimental extracts but reacted to extracts of the other environmental allergens, while the remaining fifty-two per cent gave negative reactions to all of the extracts tested. The records of the nineteen patients who gave positive reactions to the experimental *Alternaria* extracts are shown in Table III. Table IV lists the other allergens to which these patients also gave positive reactions, as well as the seasons during which the patient's symptoms occurred.

An examination of Table III shows that one patient, number 1, reacted to all the experimental extracts of *Alternaria* and related genera, i.e., extracts numbered 1-10, and four more patients, 10, 12, 13 and 19, reacted to all but one (no. 10) of these extracts. It is of interest to note that, of these five patients, all but one, number 19, reacted to the standard *Alternaria* extract. In none of the cases did a patient react to the standard *Alternaria* extract without reacting to one or more of the experimental extracts. This would seem to indicate that the experimental series of extracts was able to detect any patients who would normally give a positive reaction to the standard extract. In addition, twelve of the nineteen patients who gave positive reactions to the experimental extracts did not react to the standard extract. Under the ordinary system of testing, these would have been reported as negative. It is also important to note that, in all cases, the reactions to the experimental extracts were as large as or larger than the reactions to the standard extract. This would tend

TABLE III. REACTIONS TO EXPERIMENTAL EXTRACTS

Case No.	Extract Number												
	1	2	3	4	5	6	7	8	9	10	11	12	St'd Ext.
1	+++	+++	+++	+++	+++	+++	+++	+	+++	+++	0	0	++
2	0	0	0	0	+	0	+++	0	0	+	0	0	0
3	+	0	0	0	0	0	+	0	0	+	0	0	0
4	++	+++	0	0	0	+++	+++	++++	++++	+++	0	0	0
5	0	0	0	0	0	0	+++	0	0	0	0	0	0
6	+++	0	+++	0	0	0	0	++++	0	0	0	0	0
7	++++	++++	++++	++++	0	++++	0	++++	++++		0	0	0
8	++++	0	0	+++	++++	+++	0	+++	0		0	0	++
9	0	0	0	+++	0	+++	+++	++	+++		0	0	0
10	++	+++	+	+++	++	++++	++++	++	++		+++	++	+
11	+++	+++	0	0	0	0	0	0	0		0	0	0
12	++++	++++	++++	++++	++++	++++	++++	++++	+++		0	0	+++
13	+++	+++	+++	+++	++++	+++	+++	+++	+++		0	0	++
14	+++	0	0	0	0	0	0	0	0		0	0	0
15	+++	+++	0	+	+++	++	++++	+++	+++		+++	0	+
16	0	0	0	0	0	0	0	0	++++		0	0	0
17	0	0	0	0	0	++++	0	0	++		++++	0	+
18	+++	++++	0	++++	0	0	0	0	+++		0	0	0
19	+++	++++	++	++++	++	+++	++++	++++	+++		0	0	0
Totals +	14	10	7	10	8	11	11	11	12	4	3	1	7
0	5	9	12	9	11	8	8	8	7	2	16	18	12

to indicate that the experimental extracts are somewhat stronger than the standard extract and still do not appear to be irritative. If the experimental extracts are irritative then one might expect to find more patients reacting to the same group or combinations of extracts. An examination of Table III shows that this was not the case; in fact, other than the patients who reacted to all of the first nine experimental extracts, none of the patients showed reactions to the same combination of extracts.

Another important observation, as evidenced by the data in Table III, is that a positive reaction to one isolate of *Alternaria tenuis* was not necessarily accompanied by positive reactions to all isolates of *Alternaria tenuis* even though, as accurately as can be determined, these isolates are all taxonomically identical. In fact, it is interesting to note that a reaction to one of the extracts of *A. tenuis* of local origin did not insure a reaction to the extract of the other local isolate of this species. Patients 1, 10, 12, 13 and 19, however, reacted to all extracts.

DISCUSSION

The clinical work reported in this investigation brings out some interesting points in regard to the incidence of positive reactions to fungi as observed among children. Twenty-five per cent of the patients gave positive reactions to one or more species of *Alternaria* and related genera. Harsh and Allen,[10] in San Diego, reported 25 per cent positive reactions to fungi, but they included reactions to fungi other than the genus *Alternaria*. In a mixed group of adults and children they found 18 per cent positive reactions to *Alternaria*. For children alone, this percentage would very likely be higher since many workers, including Feinberg,[6] Lamson and Rogers,[13] and Pennington[16] report that children give more positive reactions to fungi than do adults. Pratt,[17] working at Children's

TABLE IV. REACTIONS TO ENVIRONMENTAL ALLERGENS AND SEASONAL EXACERBATION OF SYMPTOMS

Case No.	Environmental Allergens which Gave Positive Reactions	Winter	Spring	Summer	Fall
1	Alternaria		S		S
2	Grasses, Ragweed	s	s	s	s
3	House dust	s	s	s	s
4	Grasses, Ragweed				S
5	House dust	s	s	s	S
6	Ragweed, House dust				S
7	Alder, House dust, Rabbit				S
8	Alternaria, Ragweed, Dust				S
9	Dust, Kapok, Elm, Cat				S
10	Alternaria, House dust		S		S
11	House dust	s	s	s	s
12	Alternaria, House dust	s			S
13	Alternaria	s			S
14					S
15	Alternaria, Dust, Ragweed				S
16		s	s	s	s
17	Alternaria, Dust, Flaxseed	S			S
18	Dust				S
19		S	s	s	S

S—Intense symptoms.
s—Usual symptoms.

Hospital of Boston, also found that 25 per cent of the children gave positive reactions to intradermal tests with *Alternaria* extract.

At first glance, the results of Pratt and of Harsh and Allen would appear to be very close to the results which were obtained in the present work; however, it must be remembered that these investigators used only one extract, whereas in the present work, extracts of several species were used. If only one extract had been used in this study, the percentage incidence of positive reactions could have varied from 10 per cent to 18 per cent depending on the species used to prepare the extract.

The lower incidence of positive reactions that were obtained with the experimental extracts might mean that the extracts which were used were weaker than those that were used by other workers. This does not seem likely since these experimental extracts always gave reactions as great as or greater than the standard extract which was prepared and standardized according to accepted methods.

The difference in the incidence of positive reactions may be due to the difference in ability of other species to elicit positive reactions. This is a difficult point to resolve, since, even with authentic identification of species, reactions to different isolates or physiologic strains of the same species is not always the same.

It was hoped that the results of the present study would point to a higher specificity of the experimental extracts as compared to the standard extract. The results, as recorded in Table III, show a limited degree of specificity but nothing comparable to the high specificity reported by Rackemann et al[21] in the genus *Cladosporium.* As already observed, individual patients do not react to all isolates of the same species. It is also evident that sensitivity is not exhibited to the entire genus.

In regard to the ability of the experimental extracts to elicit specific reactions, one must consider the reactions to other allergens as recorded

in Table IV. In this study the reactions to the experimental extracts were, in all cases but one, as great as or greater than the reactions to any of the other allergens. This one case was quite definitely a case of ragweed sensitivity as evidenced by a greater reaction to ragweed and by the very precise season during which the patient was troubled. Frequently the reaction to the other allergens could be ruled out, as in the case of patient No. 7. This patient gave positive reactions to Alder pollen, house dust, and rabbit dander, in addition to positive reactions to some of the experimental extracts. The seasonal sensitivity of the patient would rule out Alder pollen which is not present in the fall. Dust and rabbit would probably not be seasonal, hence, *Alternaria* must be considered important.

The cases in which the patients are troubled perennially and react to other allergens may be interpreted as multiple sensitization.

In general, no far-reaching conclusions can be drawn from these experiments. Specific sensitization to particular species of *Alternaria* is certainly not clear cut, and the conclusion that all *Alternaria* species contain a common excitant is also not substantiated.

The use of sonic energy to liberate the allergen from the fungus during preparation of the extracts appears to yield a more specific preparation than do standard methods of preparation. However, it is increasingly evident that reliable methods of standardization are needed before different extracts, even those prepared with the utmost precaution by identical methods, can be compared as to biological activity.

SUMMARY

1. Sonic vibrations of 9,000 cps were used to rupture the cells of fungi for the preparation of extracts for skin testing.

2. Extracts were prepared by this method from ten species and strains of *Alternaria* and related genera and from isolates of a *Cladosporium* sp. and an *Epicoccum* sp.

3. These extracts were routinely tested along with other allergens on allergic children. Twenty-five per cent of the children reacted to one or more of the experimental extracts.

4. The extracts appeared to be potent, specific, and non-irritative.

5. There was no indication that extracts of any one species or any one isolate of a species would give a reaction in all sensitive cases.

6. There was also no indication that all species of *Alternaria* contain a common excitant.

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FIELD SURVEY OF HAY FEVER PRODUCING PLANTS

The Allergy Foundation of Northern California has been granted funds to carry out a field survey of hay fever producing plants in northern California. This survey will be conducted over a two-year period by Professor McMinn of Mills College, Oakland. When it is completed, the results will be published for general distribution.

STATUS ASTHMATICUS IN INFANCY AND CHILDHOOD

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BY definition, we feel that status asthmaticus is that state of severe bronchial asthma, which fails to respond readily to the usual methods of therapy.[31] We prefer this definition to that of Sheldon, Lovell and Mathew,[27] who describe it as "a state in which a person experiences continuous asthma over twenty-four hours, and fails to respond to injections of epinephrine." Others[1] describe the attack of asthma as status asthmaticus, "when the attack stage has persisted for more than thirty-six to forty-eight hours, in spite of epinephrine and aminophylline."

Many text books of allergy,[31,33,34] state that status asthmaticus is quite infrequent in infancy and childhood, and most authorities agree that the mortality rate is very low. We are in accord with these statements. However, it is the experience of the authors and others[13,20,30,32] that death occurs from status asthmaticus, in these age groups—and probably more frequently than is reported.

When this disease does occur in infancy and childhood, it is more difficult to treat than its adult equivalent,[1] for the following reasons:

1. The mucosa of the tracheobronchial tree is redundant.[11] The caliber of the air conduits is small. As a result of these factors, small amounts of secretions, mild degrees of inflammation, or slight spasm or edema, will result in significant obstruction, and resistance to air flow.

2. Although the cough reflex is usually present, it is not adequately utilized.

3. Dehydration occurs more readily, because of the hydrolability of infants and children. There is increase in insensible fluid loss. This is particularly true with the fever that accompanies infection. The immature distal renal tubules of infants are unable to conserve fluids in the presence of dehydration.

4. We are of the opinion, along with others,[8,17,28] that infection is one of the most important causes of asthma in infants and children. Contrariwise, other authors[31,33] state that foods are the usual excitants in the earlier years of life, whereas inhalants, especially dust, drugs, and bacteria, are of increasingly greater significance in older children. Infection also assumes great significance because of its complicating role in status asthmaticus. Infants and children, unlike adults, are unable to localize their infection. Hence, systemic manifestations of infection are

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the rule, rather than the exception. Furthermore, bacteria ordinarily considered nonpathogenic in adults are frequently pathogenic in children.

PHYSIOLOGIC ASPECTS OF STATUS ASTHMATICUS

The initiating abnormality of the pathologic physiology of status asthmaticus is partial bronchiolar obstruction.

To maintain adequate alveolar ventilation with the increased resistance to air flow, resulting from spasm and secretions, an increase in the work of inspiration is required. Normally, the expiratory phase of ventilation is entirely passive and is mediated by the elasticity of the expanded lung. To permit the tachypnea and hyperventilation, which is universally present in these patients, expiration must become an active, forceful procedure.

The lung elasticity will not permit sufficiently rapid expiration against the abnormal resistance, in spite of the increase in lung volume. Thus, both phases of respiration require an increased muscular effort.

Variations in the degree of obstruction result in uneven distribution of the inspired air. This alters alveolar ventilation-perfusion relationships.[22] Those alveoli, that are hyperventilated, with respect to their perfusing blood, constitute an increase in the physiologic dead space. This diminishes the efficiency of total ventilation. As more blood perfuses poorly ventilated areas of the lung, arterial unsaturation increases and may be associated with carbon dioxide retention. Increasing partial pressure of carbon dioxide progressively stimulates ventilation until a maximum effect occurs. Further increases result in a progressive central nervous system depression,[6,24] with a slowing of the respiratory rate, and diminishing state of consciousness. Consequently, the patient with central nervous system depression from any cause (hypercapnea, narcotics, etc.) may maintain ventilation primarily by means of the anoxic stimulus to his carotid and aortic bodies.[5] The removal of this peripheral stimulus, by the use of high concentrations of oxygen, will decrease ventilation and further increase hypercapnea.[9,10,29]

RECOMMENDED THERAPY

Having decided that status asthmaticus is actually present or impending, prompt hospitalization is a prerequisite for its successful management.

Continuous clinical evaluation will serve as a guide in dictating the type and amount of therapy and its subsequent efficacy. Accurate appraisal of the patient with status asthmaticus involves evaluation of both local and systemic factors. Respiratory rate, degree of bronchiolospasm, amount and tenacity of secretions, and superimposed parenchymal infection are the pulmonary features to be noted. Systemically, the degree of cyanosis, state of hydration, muscular fatigue, state of consciousness, and acid-base balance require careful evaluation. With regard to the latter, an arterial blood pH and serum carbon dioxide content will show the pres-

ence of carbon dioxide retention and pulmonary acidosis. The serum carbon dioxide combining power may be elevated. The clinical impression of hypercapnea is warranted in the patient with status asthmaticus, when, lacking these studies, there is lethargy to unconsciousness, associated with a decreased respiratory rate, with or without the presence of cyanosis.

Therapy must be directed towards reinstituting adequate alveolar ventilation. This requires diminishing all factors that have contributed to increased resistance to flow, and uneven distribution, i.e., bronchiolarspasm, edema, secretions, and parenchymal infection. Although we outline below the dosage of what we consider to be the most useful drugs, the necessity for individualization is paramount.

Hydration must be adequately maintained, whether by mouth, rectum, venoclysis, hypodermoclysis, or combinations thereof. The type and amount of electrolytes chosen will be determined by the patient's clinical status. This is probably the best means of diminishing the viscosity of bronchial secretions. Fluids will also help maintain an adequate urinary output and proper muscle tonus.

Bronchodilators are of prime importance, and of these, epinephrine is the drug of choice.

Epinephrine, hypodermically, in small amounts,[1] 0.05 cc for children up to five years of age, and 0.1 cc for older patients, at regular hourly intervals, should be continued as long as bronchial obstruction is clinically evident. It is to be discontinued as soon as epinephrine-fastness develops. It may be tried again every twelve hours until a response occurs, then hourly injections of the drug may be reinstituted.

Aminophylline should be used concomitantly with epinephrine. It has a prolonged bronchodilator effect and will tend to prevent epinephrine-fastness.[18] Aminophylline is best given in the intravenous fluids, slowly, so that each dose is prolonged over a six- to eight-hour interval.[15] The individual dosage will vary with the patient's age. For infants up to one year, 0.12 grams seems appropriate. The older infant and child up to five years requires 0.25 grams. Above this age group, we use 0.5 grams. Aminophylline in a small retention enema, or by suppository, is next best. In our experience, its use by mouth is of little value. Intramuscularly, it is of some effectiveness, but causes painful local irritation.

We believe that the use of antihistamines, or ephedrine, is of little or no value in relieving status asthmaticus.

Expectorant drugs should be administered. Just as soon as asthmatic patients stop coughing up their sputum, serious mucous plugging develops. Iodides should be tried orally, such as potassium iodide (saturated solution) 0.2 cc four times a day, or in the intravenous solution, as sodium iodide, using 0.15 to 0.3 gram. Syrup of ipecac—4 cc every ten minutes for four doses, or until vomiting occurs, is of particular value in infants.[21]

The inspired air should be of a high moisture content to help liquefy the viscid secretions in the bronchi, and aid their resorption.[4] Newer

techniques involve the use of "cold steam," which serves the same purpose as conventional steam without the deleterious effects of heat.

In the main, oxygen therapy is not only indicated, but it is safe, regardless of the mode of administration. It may be combined with helium gas. In the presence of central nervous system depression, the use of oxygen becomes a double-edged sword. Hypoxia is still present and requires alleviation. At the same time, complete relief of hypoxia will remove the peripheral stimulus to respiration from the carotid and aortic body reflexes, which appears to predominate at this time. When continuous high concentrations of oxygen are administered under these circumstances, the patient "pinks up," but progresses through lethargy and coma unto death. For this reason, when the respiratory stimulus is inadequate, or where its status is in question, lower concentrations of oxygen (30 to 50 per cent) should be administered intermittently with repeated re-evaluation of the patient. Where hypoxia is severe, and oxygen administered by any of the standard methods results in a depression of consciousness, with or without decreased respirations, the use of artificial ventilation is required.

Suitable antibiotics to control any infection are of great value. Penicillin has been used extensively.[3] In infants and children, however, because of the pathogenicity of a greater number of organisms, we feel the use of a broad spectrum antibiotic is of more value. One that can be administered intramuscularly or intravenously is preferable.

Bronchoscopy may be indicated where the secretions are extremely thick and viscid and cannot be raised by other means. Many authors[16,25,35] advise against its use in the presence of pulmonary infection where dissemination of organisms may occur.

ACTH, cortisone, and hydrocortisone have a definite role in the effective control of the severely ill asthmatic patient. It is quite logical to believe these drugs should be used early, once status asthmaticus has failed to respond to epinephrine, aminophylline, adequate hydration, and antibiotics. Rose[23] states that it is the severity of the disease rather than the age of the child that determines the size of the dose. Fontana[12] feels that infants and children react to ACTH and cortisone essentially as do adults, except that they require larger doses in proportion to their body weight. The most satisfactory method of administering ACTH is by the intravenous route[26] over a prolonged period. Ideally, an ACTH blood level should be maintained by a continuous intravenous drip.

ACTH—20 units in the intravenous fluids should run for a period of at least six, and preferably twelve hours. This should be followed immediately by a similar quantity and continued until all signs and symptoms disappear, or serious untoward side-effects warrant its discontinuance.

Oral or intramuscular cortisone or hydrocortisone (and present opinion seems to favor hydrocortisone) may be used concomitantly with ACTH, or alternating with ACTH, or by itself—50 mg every six hours

for an infant, and larger doses as required, may be indicated. Currently, it is thought that the intravenous administration of hydrocortisone (free alcohol) may act faster and hence may be the best drug to use in this condition.

Segal[3] points out that there seems to be a law of diminishing returns with the repeated courses of this therapy, so that the third or fourth course of ACTH or cortisone gives far less effective results than the first one. Consequently, initial doses should be maximal.

As a result of the use of ACTH or cortisone, Rose,[23] notes that changes occur in the bacterial flora of the respiratory tract and in the blood. Hence, it is quite logical to assume that the type of antibiotic used to control the "triggering," or the complicating infection, may have to be changed. It has been noted[3] the danger of infection is greater when ACTH has been used. Segal and Barach[3] feel that penicillin is the drug of choice to control this infection.

The main drawback in the use of ACTH or cortisone, is the delay in body response that occurs. Arbesman et al,[2] found a time lag in maximum response in the use of intravenous ACTH, of seventy-two to ninety-six hours after starting therapy; Lockey et al,[19] found a time lag of twenty-four to seventy-two hours.

Hence, while most authors are agreed upon the value of ACTH or cortisone, none have suggested what is to be done in the time interval before the steroids evoke their peak therapeutic effect. It is during this interval, we are convinced, that many children die. Wishful expectancy seems to be the current policy, and we believe it is the wrong philosophy.

We propose that, during this time interval, a life-saving measure may well be the use of intermittent positive pressure breathing of the inspiratory type (IPPB/I). It is the one therapeutic tool that can be employed while we are awaiting the effect of other therapy. We do not suggest by any means that other treatment be discontinued. Rather, this is one more adjunct in the armamentarium of therapy for status asthmaticus.

Artificial ventilation becomes a life-saving measure in the presence of progressive carbon dioxide retention. When the ventilatory stimulus is inadequate, an automatic respirator must be used. While spontaneous respirations are still present, we prefer the use of IPPB/I. Intermittent positive pressure breathing (IPPB), of the type delivered by Bennett or Emerson machines, plays a definite role in correction of the pathologic physiology of status asthmaticus. Compressed gas is delivered by means of a face mask, mouthpiece, or endotracheal tube, up to adjustable peak pressures, during inspiration only. Ventilation is initiated and terminated by the patient's voluntary respiratory effort. This facilitates a greater tidal air at the patient's own respiratory rate. The mask pressure curves of the machine show that the positive pressure is built up more slowly than it is released. Its over-all effect is to raise secretions. This is similar to the voluntary cough. Both machines have nebulizer attachments through

which bronchodilator drugs may be most efficiently dispersed into the bronchial tree. IPPB, therefore, increases alveolar ventilation, permitting an increased carbon dioxide excretion. Inspired air is more evenly distributed, which decreases venous admixture. Treatment with IPPB should be continuous, so long as the effect of carbon dioxide narcosis, severe anoxia, viscid secretions, or over-sedation are present. The Bennett machine can be operated manually, should apnea be present.

The duration of treatment is governed by the patient's response. It should be employed as frequently and as long as the patient will tolerate the machine, until the state of consciousness improves. Care must be exercised, particularly where depression is due to drug therapy, that excessive excretion of carbon dioxide does not occur, or else the patient may become alkalotic and tetanic. IPPB/I is not reserved for the patient in "extremis." It can be given early in the course of the disease so as to shorten the duration of the attack, conserve muscle strength, and diminish the incidence of complicating infection. Treatments, approximately every two to three hours, for ten minutes will usually suffice. The peak pressure will depend upon the age of the patient, respiratory rate, and individual tolerance to the procedure. Starting at a peak pressure of 10 cm of water, it may be increased to 12, 15, and even 18 or 20 cm. Slow, deep, respirations are more efficient. It is advisable to train the child during an interval phase. This will acclimate the patient and dispel fear of the procedure when it should become necessary.

Goddard[14] uses aerosol therapy almost routinely, along with IPPB/I in the treatment of infants with severe asthma and pulmonary insufficiency. He reports twenty-three out of twenty-four children were benefited with improvement varying from 50 to 100 per cent. There were 245 treatments given without any adverse effects.

CASE HISTORY

J. M., the daughter of a physician, was first seen at birth. Asthma, hay fever, and eczema were present on both sides of the family, and a younger sibling had eczema. Cutaneous eruptions were manifested before the age of one year, clinically thought due to milk, wheat, and penicillin, respectively. At twelve months the patient acquired a right upper lobe pneumonia for which she was hospitalized and given Terramycin.® The diagnosis was confirmed by x-ray. For the first time bronchial asthma appeared, which responded well to injections of epinephrine. At fourteen months, and every month thereafter, child experienced an attack of asthma, predominantly following respiratory tract infections. On each occasion, patient was relieved by hypodermic epinephrine.

At the age of 19 months, while in Europe, child developed an upper respiratory infection and became critically ill. She was hospitalized with status asthmaticus and right middle lobe pneumonia. For the first time, epinephrine-fastness occurred, and her condition became progressively worse. ACTH was given, with improvement, and the child was then flown back to the United States.

She was admitted to the hospital on December 21, 1953, at the age of twenty months, because of persistent asthma. Physical examination revealed the presence

of a mild upper respiratory infection, sinusitis, and bronchial asthma. Shortly afterwards, an acute otitis media occurred.

Intradermal skin tests were performed. Neither epinephrine nor aminophylline was permitted for at least four hours before testing. The results of skin testing showed slight positive reactions to house dust and milk, and negative reactions to the other allergens, including bacteria and molds. X-rays revealed chronic sinus disease, but normal chest findings.

A complete blood count showed: hemoglobin 13.5 grams, RBC 4,320,000, WBC 6700, with 24 per cent neutrophils (all segmented forms), 61 per cent lymphocytes, 2 per cent monocytes, 11 per cent eosinophils, and 2 per cent basophils. Treatment consisted of hydration, steam, Proetz regime, epinephrine at frequent intervals, Terramycin by mouth, and aminophylline by rectum.

On December 27, 1953, the nasal discharge became frankly purulent. Asthma was more intense, but still responded to epinephrine. At 7:00 p.m., on the same day the patient became epinephrine-fast. She was in croupette, receiving Alevaire® mist intermittently. On December 28, at 2:00 a.m., she became stuporous, and was given 720 cc of 10 per cent glucose in water, along with 0.2 grams of aminophylline. Forty units of ACTH were administered intramuscularly at 3:30 a.m. Her pulse was 156, blood pressure 104/70, and respiratory rate 60/minute. Temperature was 102° rectally. The carbon dioxide combining power, taken at 4:00 a.m., was 44 volumes per cent. At this time chest x-ray revealed only marked emphysema. By 9:00 a.m., the child appeared moribund. Respirations were 62/minute. Patient was comatose and would not respond to external stimuli. She would become cyanotic immediately upon removal from the croupette.

Intravenous therapy with 20 units of ACTH, aminophylline 0.25 grams, and 1000 cc of 5 per cent glucose in water, was continued by slow drip. Intermittent positive pressure of the inspiratory type with the Bennett apparatus was started. The peak pressure was set at 12 cm of water. The patient received three courses of IPPB/I for five minutes each. Following the second treatment, the state of consciousness improved, so that she began to cry and respond to external stimuli. At 1:00 p.m. her state of consciousness had returned to normal, and the degree of bronchial obstruction had diminished. At this time, she manifested a febrile response of 103° rectally, for which she was given 100 mg of Terramycin intravenously. By 7:00 p.m. all the signs of status asthmaticus were gone.

A complete blood count on December 28, 1953, showed hemoglobin 12.1 grams, RBC 4,120,000, and WBC 11,600. The neutrophil count was 82 per cent, of which seventy-four were segmented and eight were non-segmented forms. The lymphocytes were 18 per cent.

On December 30, 1953, the hemoglobin was 12.4 grams, RBC 3,930,000, with WBC 14,400. The neutrophil count was 36 per cent of which thirty-four were segmented and two were non-segmented forms. The lymphocytes were 50 per cent, and eosinophils were 14 per cent.

The child continued to improve, and was maintained on Terramycin, 500 mg per day, Streptomycin® 700 mg intramuscularly, along with epinephrine, and occasionally intravenous aminophylline, plus five per cent glucose in water. Her chest x-ray on December 30 was negative.

On January 7, 1954, bronchoscopy was performed with negative findings. A culture was taken and a pure growth of *Staphylococcus Aureus* developed.

It is to be noted that the patient fulfills all the criteria of Buffum[7] for the diagnosis of asthma in infancy.

The child was discharged, symptom free, on January 10, 1954.

CONCLUSION

When status asthmaticus occurs in infants and children, it is more difficult to treat than its adult counterpart.

An understanding of the basic pathophysiology is a prerequisite for the rational and successful management of the patient. Early recognition of status asthmaticus, and the need for hospitalization is emphasized. Classical regimens of treatment involve standard doses of drugs. The importance of individualization of treatment in infants and children cannot be overstressed. Adequate logical routine therapy will be successful in the vast majority of cases. In those instances where the patient fails to respond, the use of ACTH or cortisone is indicated. Decreased response to repeated courses occur with these drugs. Hence, they should be withheld until indicated, and then used in maximal doses. There is a time interval of twelve to ninety-six hours between initiation of steroid therapy and peak body response.

Intermittent positive pressure breathing of the inspiratory type plays a definite role in the correction of the pathophysiology of status athmaticus.

Where adequate routine management fails, and especially where steroid therapy has been instituted, and has not yet effected a favorable response, then the use of IPPB/I is mandatory, and may be life saving. When the ventilatory stimulus is markedly depressed, whether due to severe hypoxia, carbon dioxide retention, or over-sedation, the use of the automatic respirator is necessary.

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SECOND AIR POLLUTION OFFICER NAMED

Louis C. McCabe, nationally known air pollution authority, has been called to active duty as a commissioned officer of the U. S. Public Health Service, and will serve as staff advisor on air pollution to Assistant Surgeon General Mark D. Hollis, Chief Sanitary Engineer of the Service and Chief of the Division of Sanitary Engineering Services.

This is the second major appointment in air-pollution-control activities filled by the Public Health Service this year. Recently, Arthur C. Stern, formerly Chief Industrial Hygiene Engineer of the New York State Department of Labor, assumed direction of the program of air pollution research and technical assistance to state and local agencies.

Dr. McCabe, who will have headquarters in Washington, will be responsible for technical staff activities and program liaison with other federal agencies.

SOYBEAN: ANAPHYLACTOGENIC PROPERTIES

BRET RATNER, M.D., F.A.C.A. and LLOYD V. CRAWFORD, M.D.

New York, New York

THE question of the allergenicity of soybean aroused interest a number of years ago when Duke,[1] in 1934, reported a case of an individual exquisitely sensitive to soybean. He pointed out that his patient had lived and worked near a soybean mill. In addition, he reported five cases of persons actually working in the mill who suffered from asthma and who were found allergic to soybean extract.

While the possibilities for utilization of soybean are many and the production of soybean has increased greatly during the past years, the major portion of the crop is used for the production of soybean oil and meal. About 85 per cent of the oil goes into food uses while only about 10 per cent of the meal is utilized for food and industrial purposes. Whole soybeans are used in making soybean milk which is used principally for feeding infants who are allergic to cow's milk. A specially prepared meal is converted into soy flour and thus may be a hidden source of contact in breadstuffs, cakes, crackers, cereals, noodles and macaroni as well as sausages and confections. A new product, Gelsoy, which has some properties of egg white, has potential applications in such foods as frozen desserts, sausages and candy, and as a special sealing adhesive. In industry the soybean meal is utilized to make glue for the fabrication of plywood and the isolated protein is used extensively for sizing and finishes for paper, in paper lamination, and in latex paints. The meal is our most important source of protein concentrate for animal feeds.

Undoubtedly, as more economically feasible methods are developed for the extraction of the soybean protein, more industrial uses will be devised. At present the chief hazard, from the allergic standpoint, would seem to be that of inhalation of soybean dust in the oil-processing factories.

Despite Duke's warning that soybean might become a source of allergy, there has been practically no evidence in the literature in the intervening twenty years that soybean is an important factor in this disease. Hill,[5] in 1942, deduced from his studies that soybean is a poor antigen.

Because of the use of soybean as a milk substitute in infant feeding, we undertook to investigate it from the standpoint of its allergenicity. Our work is reported in two papers. The first paper is concerned with its

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Dr. Crawford, Research Fellow in Pediatric Allergy, is now in Memphis, Tennessee.

This is Number VI of a series of studies on Anaphylactogenicity of Modified and Processed Foodstuffs, supported in part by a grant from the Playtex Park Research Institute. The technical assistance of Kathryn M. Mayer and Joseph S. Thomas in the prosecution of these experiments is hereby acknowledged with appreciation.

allergenicity in the human subject.[6] This one presents a study of the anaphylactogenicity of soybean in the guinea pig.

MATERIALS AND METHODS

The materials used were raw dried soybean, soybean flour* and soybean extract.

Soybean Extract.—The soybean extract (SBE)** was prepared as follows: Raw dried beans were chopped thoroughly and reduced to a powder by grinding. The excess fat and oil were removed by treatment with acetone. The material was then extracted with N/10 NaOH solution. It was neutralized with dilute HCl and the resultant precipitate dried and sifted. A weighed amount of this mixture was suspended in N/20 NaOH solution. The suspension was centrifuged, decanted and the residue exhausted by successive extractions with N/20 NaOH solution. The extractions were combined and filtered until clear. To the filtrate was added ¼ volume of a solution containing in each 100 cc di-sodium phosphate 1.43 g and mono-potassium phosphate 0.363 g. The reaction of the resultant solution was adjusted to pH 8.3 by addition of either HCl or NaOH solution. Cresol in proportion of 0.4 per cent was added and the solution sterilized through a Berkefeld filter.

This extract contained 0.87 mg protein nitrogen per cc and was used in 1:100 dilution for the anaphylaxis experiments except where otherwise noted.

Soybean Flour.—The soybean flour for the inhalation experiments was defatted with anhydrous ether.

Freund's Adjuvant.[5]—In a series of animals Freund's Adjuvant† was used in order to enhance the sensitizing properties of the soybean extract and was made in the following manner:

The emulsifying agent, Arlasel-A (Atlas Powder Co.), and oil (Botol-F, Esso Gas Co.) are mixed in the proportion of 1.5 to 8.5 parts. Dried *Mycobacterium butyricum* is added to the above in amounts of 8 to 10 mg per cc. On the day the antigen is to be used, one part of the antigen solution is added to three parts of adjuvant and well mixed.

Animals.‡—Guinea pigs weighing approximately 250 g were used and were fed on regular animal rations.

Specially bred animals were employed in certain of the experiments.

*Special X Brand, manufactured by Spencer Kellogg and Sons, Inc.

**This material was kindly made for us by Seymour L. Shapiro, Director of Biological Laboratories, Arlington Chemical Company, U. S. Vitamin Corporation.

†This material was kindly supplied to us by Dr. Jules Freund.

‡All animals were procured from Carworth Farms, New City, N. Y.

TABLE I. EXPERIMENTS WITH ANIMALS FED RATIONS CONTAINING SOYBEAN

Number of Animals	Sensitizing Injection Ip.	Shock Injection with SBE*, Iv.	Results
41	1 cc SBE single dose	0.3 cc	0
18	4 doses each of 2 to 4 cc over a period of 8 days	0.1 to 0.3 cc	0
7	1 cc of a mixture of SBE & Freund's Adjuvant in proportion of 1:4	0.3 cc	4 animals 0 1 animal + 1 animal ++ 1 animal ++++

*SBE soybean extract. In this and the following tables, unless otherwise specified, the dilution is 1:100.
+—moderate dyspnea.
++—dyspnea and convulsions.
++++—anaphylactic death with typically ballooned lungs.

TABLE II. EXPERIMENTS WITH ANIMALS FED SOYBEAN-FREE RATIONS*

Number of Animals	Sensitizing Injection SBE, Ip.	Shock Injection SBE, Iv.	Result
14	Total of 1.5 cc in 2 doses 3 days apart	0.3 cc (1:100)	0
9	Total of 2 cc in 4 doses within 7 day period	0.3 cc (1:100)	8 animals 0 1 animal ++
2	"	0.3 cc (1:50)	0
5	"	0.3 cc (1:20)	2 animals 0 2 animals + 1 animal ++++

*The mothers were also maintained on soybean-free rations prior to and during pregnancy.

They were the offspring of female guinea pigs which, prior to and throughout their pregnancy, were maintained on a diet containing no soybean. The offspring were also continued on the soybean-free diet.

Anaphylaxis Procedures.—The anaphylaxis method employed was fully described in a previous paper[9] of this series. All sensitizing injections were given intraperitoneally and the challenging dose was given intravenously, except where otherwise stated, three or more weeks later.

The inhalation experiments were carried out as previously described,[7] using defatted soybean flour. The animals were exposed in a specially constructed cage and after a suitable incubation period were re-exposed to the inhalation of soybean flour. They were subsequently challenged with an intravenous injection of soybean extract.

EXPERIMENTAL RESULTS

Parenteral Injection Experiments.—Table I presents a total of sixty-six guinea pigs. Forty-one of these animals, fed regular rations, each received a single sensitizing injection of 1 cc SBE and was challenged with 0.3 cc of the same substance three weeks later. This group gave no evidence of having been sensitized.

We then attempted to reinforce the sensitizing exposure and gave each of eighteen animals four sensitizing injections of from two to four cc over a period of eight days. Three weeks later they were challenged with SBE and there was no evidence of the establishment of sensitization.

TABLE III. INHALATION EXPERIMENTS WITH DRY DEFATTED SOYBEAN FLOUR

Number of Animals	Sensitization	Shock	Results
10	A total of 7 hours of inhalation exposure to dry soybean flour over a period of 5 weeks	15 minute inhalation 1 hr. later 0.1 cc 1:20 SBE, Iv.	0 0

Seven animals were each sensitized with 1 cc of the soybean antigen incorporated in Freund's Adjuvant (1:4). Of these, three demonstrated typical shock reactions but in only one was the reaction profound enough to result in anaphylactic death.

Table II shows the results of experiments on a total of thirty animals. Of these specially bred animals, fourteen were given 1.5 cc SBE 1:100 in two doses, three days apart. When they were challenged three weeks later with 0.3 cc SBE 1:100, no evidence of sensitization appeared.

Nine of these specially bred animals each received a total of 2 cc in four sensitizing injections of SBE 1:100 within seven days in an attempt to reinforce their sensitization. They were challenged with 0.3 cc SBE 1:100. One animal showed a + + anaphylactic reaction, the other eight were negative.

Two of these specially bred animals were sensitized in the same manner as the above and were challenged with an injection of 0.3 cc SBE 1:50 (twice the concentration given the previous group) with negative results.

Five additional animals, similarly sensitized, were given a shock injection of 0.3 cc SBE 1:20 (five times the concentration given the nine guinea pigs) and of these, three reacted, one of them dying a typical anaphylactic death.

It is apparent from this series of experiments that the food of the animal is not the dominant factor in this resistance to sensitization with soybean.

Inhalation Experiments.—Because of instances of sensitivity to soybean in human subjects caused by the inhalation of soybean dust in the proximity of soybean processing factories, an attempt was made to sensitize animals through inhalation.

Table III records the results of experiments on ten animals which were exposed in the inhalation chamber to dry defatted soybean flour for a total of seven hours, over a period of thirty-five days. After a rest period of three weeks these animals were again challenged by an inhalation exposure to soybean flour. The results were uniformly negative. Following the technique of the double shock method, which we have previously described,[9] the animals were then challenged for the first time with an intravenous injection of SBE and they were still negative.

We have no doubt that had we persisted in this laborious work we might

have shown evidence of occasional sensitization. This would serve no further purpose, however, than to show that the soybean, whether injected or inhaled, has a low order of antigenicity.

COMMENT

An analogous series of unpublished experiments was kindly given to us for report in this paper by Dr. Henry Stevens.§

We were not cognizant of this unpublished work when we planned and carried out our studies. They parallel our experiments so closely that we deem them a valuable addition to our presentation. The results were tabulated by Dr. E. J. Coulson of Dr. Stevens' department, from experiments done in 1943 and they support our thesis of the weak antigenicity of soybean.

These investigators carried out their experiments on guinea pigs sensitized to an extract made from ground and defatted soybeans. The Schultz-Dale tests was used exclusively to determine sensitization. They found: (1) that the antigens of soybean were too weak to provide satisfactory guidance for chemical fractionation; (2) that soybean-free rations did not perceptibly increase susceptibility of the guinea pigs to sensitization; (3) that for one small group of animals multiple sensitizing injections accomplished sensitization, but afforded no impressive advantage; (4) and that sensitization was enhanced by injection of alum-precipitated soybean extracts. They concluded that soybean was a weak antigen.

In our experiments we did not find any instance of sensitization in a large number of animals after a single sensitizing dose followed by an intravenous challenging dose. We were further unable to sensitize animals in which, instead of a single injection, as many as four sensitizing injections were given.

When we resorted to sensitization with soybean extract incorporated in Freund's Adjuvant, which enhances sensitization with weak antigens, we were able to produce actual anaphylactic shock. This further demonstrates the allergenic weakness of soybean with which we are concerned, for only when an adjuvant was used to reinforce antigenicity did we get an instance of anaphylactic death.

The thought that perhaps the weak antigenicity might be attributable to the establishment of immunity in the animals through the ingestion of soybean in the food rations of the mother and offspring led us to the use of specially bred animals. Mothers were fed prior to and throughout pregnancy on a diet consisting of oats and vegetables with the complete exclusion of soybean, to minimize the possibility of placental passage of soybean antibodies which might cause an immunity. The offspring of these mothers were similarly fed on a soybean-free diet.

These specially bred animals showed an extremely low degree of sen-

§Head, Allergens Section, U. S. Department of Agriculture, Agricultural Research Service, Washington Utilization Research Branch.

sitization for only one of twenty-three had a moderate anaphylactic reaction even after repeated sensitizing injections. This single example of sensitization among the specially bred animals suggests that perhaps the absence of soybean in the diet may have some minor influence. However, there was no striking difference in susceptibility between these specially bred animals and those fed on the regular food rations. It was only when we concentrated the antigen considerably that we found a single example of anaphylactic death.

In the final experiment we subjected animals to the inhalation of soybean flour for a period shown in previous studies with various other allergens to constitute an adequate exposure for this method of sensitization.[8] The animals in this present series showed no manifestation of sensitization when later exposed, after a proper incubation period, to soybean flour inhalation, nor to subsequent intravenous injection of SBE.

We believe that these experiments give evidence that soybean is innately a weak sensitizing protein.

We have previously reported on experiments concerned with the antigenicity of peanut,[11] orange,[9] and egg[10] proteins in which the majority of animals manifested evidences of sensitization to these substances. The same methods of protein extraction, the same laboratory procedures and the same source of animal supply were employed.

We have no valid explanation for the low antigenicity of soybean antigen used in these animal experiments. A possible answer may be found in the fact that there is a reduced amount of available methionine in the soybean protein.[2,4]

SUMMARY AND CONCLUSIONS

1. Soybean was demonstrated to be a weak anaphylactogen when tested in the guinea pig.

2. The weak antigenicity is moderately enhanced when adjuvants are incorporated in the soybean antigen.

3. Sensitization was not materially increased by multiple sensitizing injections.

4. Sensitization of guinea pigs was not accomplished through the inhalation of soybean flour.

5. A possible immunity acquired by the guinea pig through the habitual ingestion of soybean is a negligible factor in the degree of susceptibility of the animal to soybean sensitization.

6. The reduced amount of methionine present in the soybean protein might in part account for the lowered antigenic activity of soybean.

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50 East 78th Street
(Dr. Ratner)

SOUTHEASTERN ALLERGY ASSOCIATION

The Southeastern Allergy Association held its annual meeting at Orlando, Florida, March 25 and 26, 1955, and elected the following officers:

Ben Miller, Columbia, S. C. ..... President
Clarence Bernstein, Orlando, Fla. ..... President-elect
Charles Wofford, Johnson City, Tenn. ..... 1st Vice President
Andrew D. Taylor, Charlotte, N. C. ..... 2d Vice President
Frederick Hieber, St. Petersburg, Fla. ..... Committeeman-at-large
David Thomas, Augusta, Georgia ..... Committeeman-at-large
Katharine Baylis MacInnis, Columbia, S. C. ..... Secretary-Treasurer

The 1956 annual meeting, which will be held in Charlotte, N. C., October 5 and 6, will have as its theme "Allergy and Its Relation to Various Branches of Medicine and Surgery." Dr. Clarence Bernstein, 740 Magnolia Avenue, Orlando, Florida, is in charge of the program.

VASCULAR HEADACHES

ROY A. OUER, M.D., F.A.C.A.
San Diego, California

IT is not the purpose of this paper to review the problems of headache but rather to present a rational approach to the treatment of vascular headaches with respect to the prevention of attacks, and to propose methods of treating the headache attack when it occurs. New forms of medication for the relief of headache will be discussed, particularly the use of derivatives of Algin, together with ergotamine. The results of therapy with such medications will be illustrated. Algin derivatives as vehicles for various medications have previously been shown to have numerous advantages over the conventional types of preparations.[1,2,3]

CLASSIFICATION

A classification of headache will be seen in Table I and is presented in order to identify the symptom complex with which this paper will deal. The major categories of headache are the extracranial, intracranial, and systemic groups.

The extracranial headache may be divided into those pain syndromes arising from the eyes, ears, nose or throat, sinuses, middle ear and labyrinth, and the neuromuscular portions of the scalp and subcutaneous tissue.

The intracranial group includes tumors and abscesses of the brain and surrounding tissues, hemorrhage of the brain linings, infections or damage to the meninges.

The systemic group comprises a large variety of head pains and in this category there is some overlapping of definition. In general, the systemic headache may arise from allergy, glandular imbalance, metabolic defects, fevers, cardiorenal disease, neurogenic or neuromuscular abnormalities, and the psychic disturbances. Vascular headaches fall into this latter group.

VASCULAR HEADACHE

A satisfactory classification of vascular headache is shown on Table II. Classical migraine is the most common form of vascular headache. The migraine varients include the ophthalmic type, the ophthalmoplegic type, abdominal or precordial migraine, and a form of prolonged headache going under the name of status migrainus. Horton's headache, or histaminic cephalalgia, has been dealt with in detail elsewhere.

Migraine differs from histaminic cephalalgia in that the patient presents a positive family history of either headache or allergy, the attacks occur

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The author acknowledges with thanks the helpfulness and courtesy extended to him by the staff and management of the Kelco Company of San Diego, manufacturers of Algin, whose cooperation is sincerely appreciated.

TABLE I. HEADACHES — CLASSIFICATION

I—EXTRACRANIAL
- A. Ocular
  - (1) Refractive errors
  - (2) Ocular imbalance
  - (3) Intraocular disease
- B. Oral
- C. Nasal or paranasal
  - (1) Sinus
  - (2) Turbinates, ducts, etc.
- D. Aural
  - (1) Middle ear
  - (2) Labyrinths
- E. Neuromuscular
  - (1) Neuritis, myositis
  - (2) Tension
- F. Osseous
  - (1) Osteoarthritis
  - (2) Tumors, fracture, discs, etc.
- G. Traumatic

II—INTRACRANIAL
- A. Tumor
- B. Abscess
- C. Hemorrhage
  - (1) Extradural
  - (2) Subdural
  - (3) Subarachnoid
  - (4) Intracerebral
- D. Infection
  - (1) Meningeal, etc.
- E. Lumbar puncture

III—SYSTEMIC
- A. Allergy
  - (1) Allergic headache
  - (2) Migraine
- B. Endocrine
  - (1) Migraine
  - (2) Menstrual, menopausal
  - (3) Pituitary, thyroid, etc.
  - (4) Hypoglycemic
- C. Metabolic
- D. Febrile
- E. Cardio-renal
  - (1) Hypertension
  - (2) Uremic
- F. Neurogenic
  - (1) Neurovascular
    - (a) Histaminic cephalalgia
    - (b) Migraine
  - (2) Neuromuscular
    - (a) Tension headache
- G. Psychogenic
  - (1) Conversions (hysterical, psychotic)
  - (2) Tension

TABLE II. VASCULAR HEADACHES — CLASSIFICATION

- I—Migraine—Classical
- II—Migraine Variants
  - A. Ophthalmic
  - B. Ophthalmoplegic
  - C. Abdominal, precordial
  - D. Status migrainus
- III—Histaminic Cephalalgia (Horton's Syndrome)
- IV—Tension Headache
- V—Arteritis (cranial vessels)
- VI—Hypertensive

early in life, an aura is present, and the attacks last many hours or days. They occur usually in the early morning, with a periodicity of a week or more between attacks, with associated symptoms of nausea and vomiting and visual disturbances.

Patients with histaminic cephalalgia present no positive family history. The disorder occurs from the fourth to sixth decades of life, has no aura, lasts less than one to two hours, occurs during the night or on waking in the morning, frequently occurs daily, with remissions between attacks, without nausea or vomiting, but associated with lacrimation, nasal obstruction and discharge, with some swelling or edema of the parts affected. Histamine desensitization is most effective in relieving the attacks of Horton's headache, while only a few patients with true migraine obtain adequate or prolonged relief from attacks by this procedure.

Tension may give rise to a vascular form of headache or a neuromyalgic form of headache. The latter is characterized by the presence of emotional stress and strain, occurs commonly on both sides of the head, in the front or back, is pressing, aching, and dull in character, is often daily or constant in type, and responds to analgesic sedation.

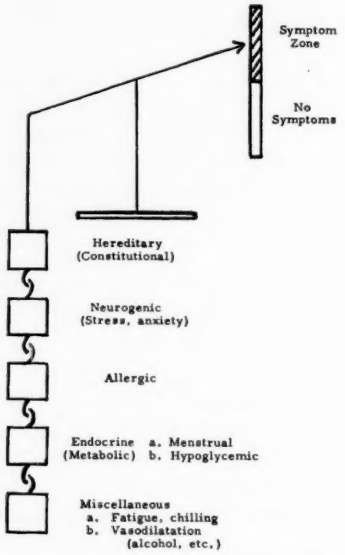

Fig. 1. Factors in migraine attack.

FACTORS PRODUCING HEADACHE

Treatment of the patient suffering from attacks of vascular headaches presents two major considerations. First, the prevention of the headache, and secondly, the relief of pain when the attack occurs.

The problem of the prevention of the attack of headache resolves itself into an attempt to eliminate or reduce the factors which may be operating to produce headache in a specific patient (Fig. 1.) These factors, or trigger mechanisms as they are sometimes called, may be present in various degrees in different subjects. The most common are the hereditary (constitutional), the neurogenic, the allergic, and the endocrine factors. Numerous other factors may be frequent initiators of head pain, such as fatigue, temperature changes, alcohol ingestion, vasodilator drugs, etc.

Depending upon the dominance of any one of these factors, or depending upon the number of such factors operating in the balance at any one time, the patient remains either in a symptom zone or in an asymptomatic zone. An interplay of these factors commonly occurs.

The hereditary or constitutional factor is present to some degree in all patients. Over 70 per cent of patients with migraine give a positive family history for allergic disorders or migraine headaches. Patients with migraine are usually tense individuals, who frequently live under emotional stress and strain. A careful investigation of the patient's environment,

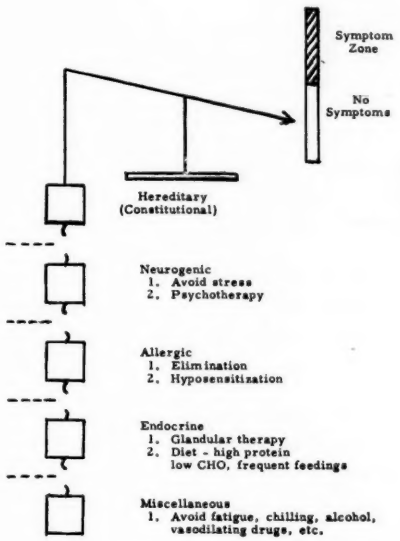

Fig. 2. General treatment of migraine.

particularly the personal contacts, and his reaction to his daily life, is often most revealing. (The sufferer is commonly a basically insecure, unhappy, or emotionally immature patient.) The specific allergic factors vary a great deal, but often the offending agents are foods, although inhalant sensitivity may produce headache in some patients. Not infrequently patients with migraine have, as a contributing factor to their headache problem, endocrine disturbances. In order to investigate the possible endocrine factors, the determination of the BMR, blood iodine and blood cholesterol values, the glucose tolerance test, the pituitary gonadotropin determination, estrogenic determination, 17 ketosteroid determination, and water balance tests should be performed. An evaluation of the function of the thyroid, pituitary, adrenal and sex glands may then be made.

It is well, therefore, to investigate the patient from several aspects: neurogenic, including psychic investigation; allergic, by elimination dietary therapeutic tests and/or skin tests; and endocrine or metabolic disturbances.

PROPHYLAXIS

After a careful analysis of all of these factors has been made, it should be possible to determine which factors are dominant in a given patient, and the exciting factors (trigger mechanisms) should have become evident. Treatment, therefore, with respect to the prevention of the attack, will be directed at any one or more of the factors present in the individual patient (Fig. 2).

Since it is not possible to change the heredity of any of these patients, nor to do much about the constitutional predisposition to headaches, this factor may very well remain in the balance, but it is possible to render patients symptom-free by removing or treating the other factors as mentioned.

It is important to have the patient remove, or adjust to, the factors in his environment which are causing emotional stress and strain. Reassurance of the patient and supportive psychotherapy will reduce the influence of the neurogenic factor.

The elimination of offending allergic agents, frequently foods, may be a tedious and time-consuming procedure, but is most important in management. Hyposensitization is usually reserved for those patients who have other allergic manifestations, such as nasal allergy or asthma, but occasionally may be of some value to patients who suffer only from allergic headaches. (Some patients will frequently have their attacks initiated by the introduction of a large dose of inhalant allergen to which they are sensitive). In those patients who have associated nasal symptomatology, antihistamines are most helpful and they also seem to be of general help in the allergic group, with respect to reducing the number of attacks.

Endocrine therapy will usually resolve itself into substitution therapy, with the judicious use of the proper hormones. Because headache patients frequently have attacks when the blood sugar is falling, or at low ebb, the diet should be high in protein, low in carbohydrate, and the patient should not go longer than four hours between feedings.

TREATMENT OF ATTACKS

In spite of following the proposed procedures for identifying and controlling the factors responsible for headaches, there will continue to be patients where the elimination of attacks has not been completely accomplished and where, from time to time, the patient will have headaches precipitated by one or more of the factors mentioned previously. In such instances, the symptomatic treatment of the attack becomes highly important.

Once the attack has begun, a rest period in a quiet, dark environment during treatment is indicated. Many patients like ice cold applications to the head. The medications of most value are the ergotamine derivatives, which may be administered orally, intramuscularly or intravenously, or rectally. Some patients find it is possible, at the onset of an attack, to abort the pain by taking one to six tablets of Cafergot,® during the prodro-

mal stage. However, many patients find that oral medication is not tolerated or is ineffective. The intramuscular use of Gynergen® is usually effective in 0.5 cc doses, and may be repeated if necessary. Dihydroergotamine is effective in a slightly smaller percentage of cases, has fewer side effects, and fewer contraindications.

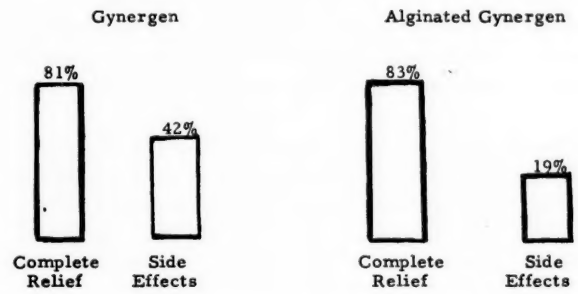

Fig. 3. Effectiveness of intramuscular medication.

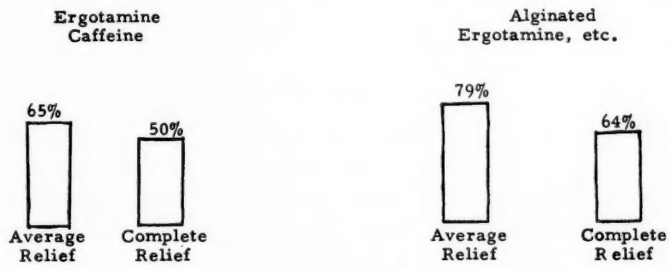

Fig. 4. Effectiveness of suppositories. Comparison in 100 attacks.

Both of these intramuscular preparations can be alginated and to date we have only used these by alginating the preparation immediately before administration. Algin derivatives have been shown previously to be nontoxic, nonallergenic, and to maintain smooth flow characteristics over wide temperature ranges, and to have several advantages over other types of vehicles.

The alginated Gynergen is apparently as effective as the aqueous preparation and the side effects by the addition of the propylene glycol ester of alginic acid have been reduced from 42 per cent to 19 per cent in an indicative group of patients (Fig. 3).

Suppository medications using algin have also been prepared and these are especially useful in patients who have difficulty with the oral or parenteral route of administration. Numerous patients, during attacks, prefer

not to go to the trouble of preparing a hypodermic medication. Others find themselves incapable of injecting themselves. There is also a group of patients who tend, at certain times, to awake over a period of several days with headache every morning. For this type of patient the suppository form is most helpful. It is also possible to alginate the ergotamine and caffeine suppositories, and a comparison of the two types of medication indicates that the alginated preparation is somewhat more effective (Fig. 4). We have not as yet worked out a satisfactory explanation for the difference in response. We suspect that there is some increase in the absorptive rate of the drug and therefore a higher blood concentration may be obtained.

In our experiments satisfactory suppositories containing ergotamine in varying amounts (approximating 2 mg), caffeine 100 mg, hyoscine hydrobromide .4 mg (to allay nausea), and sodium alginate with calcium lactate have been prepared. For hardening effect glycerol monostearate, cetyl alcohol, and carbowax have been tried. (Tri-calcium phosphate can be used as an adsorbent, if desired). Rapid absorption has been our aim, but slow absorption can also be accomplished by varying the type and concentration of the ingredients.

Modifications of these formulae are easily made, and it is hoped that with additional experimental work an ideal preparation will be made available.

SUMMARY

A rational approach to the problem of vascular headache has been presented. Suggestions for the proper classification and diagnostic approach have been discussed. Procedures for establishing a therapeutic plan, taking into account the various factors which may be constantly or intermittently present, have been outlined. The relative merits of oral, rectal, and intramuscular medications for the control of headache attacks have been discussed. A new preparation, using an algin derivative as a vehicle, has apparently resulted in the reduction of side effects in the use of intramuscular ergotamine. A new suppository medication prepared from ergotamine and caffeine using an algin derivative as a suppository base has proved most helpful.

If the physician will apply himself diligently to determining the cause of headache in a specific patient, carefully analyzing the existing factors, attempting to control or eliminate, to as great an extent as possible, these disturbing influences, and if he will work out carefully with the patient the control of headache attacks by the use of the new symptomatic medications which have been discussed, the result will be a most satisfactory relationship between the patient and his physician. This good relationship, unfortunately, is not the rule for patients suffering from vascular headaches, but as newer knowledge presents itself the outlook for this type of patient becomes increasingly brighter.

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THE ISRAEL SOCIETY OF ALLERGY

During 1954, the Israel Society of Allergy held eight scientific meetings. On January 21 in Jerusalem the meeting was devoted to a discussion of the problems of Rh-Immunization, with Prof. J. Gurewitz talking on "The Antigens Rh-Hr," Prof. A. Sadowski discussing "The Rh Factor in Pregnant Women," and Dr. J. Matot addressing the meeting on "Hemolytic Disease of the New Born." On March 10 a joint meeting was held with the medical association in Tiberias, at which Dr. M. J. Gutmann of Jerusalem lectured on "The Pollen Allergic Diseases," and the following day in a joint session with the allergy group in Haifa Dr. Gutmann discussed "Visible and Invisible Food Allergens." Dr. Gutmann substituted for Dr. I. Glaser of Tel Aviv at the March 29 meeting in Jerusalem, speaking on "Pollen Allergy in Israel."

On April 4, in Jerusalem, the Israel Society heard an address by Dr. J. Groen, Professor at the Wilhelmina-Gasthuis, Amsterdam, Holland, on "Allergic and Psychosomatic Aspects of Bronchial Asthma." With the medical association in Rehoboth, the Society on June 10 dealt with the subject of "Pollen Allergic Diseases." A "Symposium on Bronchiectasis and Bronchial Asthma" was held in Jerusalem on July 12, at which Dr. Gutmann reviewed "The Problem," Dr. M. Wollmann discussed "The Pathology of Bronchiectasis in Relation to Bronchial Asthma," Dr. S. Schor covered "X-Ray Problems of Bronchiectasis," Dr. J. Rakower talked on "Symptomatology of Bronchiectasis and its Conservative Treatment," Dr. L. Wislitzki presented "Pharmacologic Treatment of Bronchiectasis and Bronchial Asthma" and M. Milwitzki covered "Surgical Treatment of Bronchiectasis."

The Society's year closed with an address on December 13 by Dr. Paul Stern, Professor of Pharmacology at the University of Serajevo, Yugoslavia, on "Die Wirkungsweise der Antihistamine."

SUMMER BLOOMING LAMB'S-QUARTERS

A Factor in Inhalant Allergy

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A NEWCOMER in the goosefoot family, antigenically speaking, first mentioned by Stemen* and called by him "Summer Blooming Lamb's-Quarters," has become so widespread in Oklahoma that it is incriminated as a causative factor in inhalant allergy during the grass season in this area, even though the goosefoot family is believed by some to produce only appreciable amounts of mildly antigenic pollen.

It is well known that lamb's-quarters is a late summer pollinator. Even though the weed mentioned resembles very closely the regular lamb's-quarters, it differs from it botanically. This plant exudes an abundance of light buoyant toxic pollen from early June to frost, thereby paralleling the grass season as well as the amaranthus and ragweed season. It is found in abundance throughout Oklahoma and the rest of the United States, and is a heavy pollinator.

DESCRIPTION OF THE PLANT AND COMPARISON WITH REGULAR FALL BLOOMING LAMB'S-QUARTERS

This plant is one of the few which can be recognized when driving down the highway at seventy miles per hour, because of the grayish color of the leaves which are farinose on both sides. The leaves of *Chenopodium album,* or the regular lamb's-quarters, are strongly farinose beneath when young. *Chenopodium paganum Reichenb,* or summer lamb's-quarters, is not as tall, as a rule, as *Chenopodium album,* the former averaging from one to four feet in height, while the latter grows to a height of one to eight feet tall. *Chenopodium album's* branches are spreading, while the branches of the summer blooming lamb's-quarters are strongly ascending. The stems of *Chenopodium album* are usually green, while those of summer blooming lamb's-quarters *(Chenopodium paganum Reichenb)* are often purplish. The leaves of the latter are rhombic, those of the former are rhombic to broadly ovate.

Both of these plants are annual and are found throughout the United States except in the southeast and extreme west, where *Chenopodium album* only is found. *Chenopodium album,* the regular lamb's-quarters, blooms from August 15 to October 1, summer blooming lamb's-quarters *(Chenopodium paganum Reichenb)* blooms from June to October. Pollens of both are abundant, buoyant, possibly somewhat mildly antigenic, and are indistinguishable from each other.

Presented at the Eleventh Annual Congress of the American College of Allergists, Inc., April 28, 1955, Chicago, Illinois.

*Personal communication from Stemen Laboratories, Inc., Oklahoma City, Oklahoma.

TABLE I. COMPARISON OF SKIN TEST REACTIONS OF 500 ALLERGY PATIENTS

No. of Patients		Per-centages
Those patients who reacted to summer lamb's-quarters *(Chenopodium paganum Reichenb)* and NOT to regular fall lamb's-quarter's *(Chenopodium album)*	143	28.6%
Patients who reacted to regular lamb's-quarters *(Chenopodium album)* and NOT to summer lamb's-quarters *(Chenopodium paganum Reichenb)*	61	12.2%
Those who reacted to summer lamb's-quarters *(Chenopodium paganum Reichenb)* and NOT to Bermuda, Johnson, or Grama grass, or who reacted stronger to it than to the grass group	67	13.4%
Those who reacted to summer lamb's-quarters *(Chenopodium paganum Reicherb)* stronger than to the amaranthus genera	34	6.8%
Comparison of skin test reactions of summer lamb's-quarters *(Chenopodium paganum Reichenb)* and regular fall lamb's-quarters *(Chenopodium album),*		
A. Those reacting stronger to summer lamb's-quarters *(Chenopodium paganum Reichenb)*	202	40.4%
B. Those reacting stronger to regular fall lamb's-quarters *(Chenopodium album)*	107	21.4%
Comparison of summer lamb's-quarters *Chenopodium (paganum Reichenb)* to kochia		
A. Those reacting stronger to summer lamb's-quarters *(Chenopodium paganum Reichenb)*	135	27.0%
B. Those reacting stronger to kochia	90	18.0%

CLINICAL INVESTIGATION

Because of the above characteristics, it was decided to make a clinical investigation with the pollen of *Chenopodium paganum Reichenb.* Some five hundred patients with all types of respiratory allergies were skin-tested with the pollen extract of the other members of the goosefoot family, grass, amaranthus and kochia genera, which are early and midsummer pollinators. The results are shown in Table I.

Of 500 respiratory allergy patients selected at random and skin tested, 202, or 40.4 per cent, showed stronger positive skin test reactions to summer blooming lamb's-quarters *(Chenopodium paganum Reichenb)* than to fall blooming lamb's-quarters *(Chenopodium album),* while 107 of the 500 patients (21.4 per cent) showed stronger positive skin tests to the regular or fall blooming lamb's-quarters *(Chenopodium album)* than to the summer blooming variety.

One hundred forty-three patients, or 28.6 per cent, reacted to summer lamb's-quarters and not to the fall variety, and sixty-one, or 12.2 per cent, reacted positively to the latter and not to the former.

Sixty-seven patients (13.4 per cent) showed stronger positive reactions to the summer blooming lamb's-quarters than to the leading grasses of this area.

Thirty-four patients, or 6.8 per cent, showed stronger skin test reactions to summer blooming lamb's-quarters than to the amaranthus genera.

Of five hundred patients, 135, or 27 per cent, showed stronger positive skin reactions to summer blooming lamb's-quarters than to kochia, and, conversely, ninety patients (18 per cent) showed positive skin tests to kochia and not to summer blooming lamb's-quarters.

These figures show that this newcomer of the goosefoot family *(Chenopodium paganum Reichenb)* into the allergenic field reacted stronger and more frequently in 500 patients tested intradermally with a 1:1000 solution of pollen extract than did the fall blooming variety *(Chenopodium album)*.

It was also a stronger skin reactor than the grasses in sixty-seven of the 500 patients; it was a stronger reactor in thirty-four of this group than the amaranthus genera, and compared with kochia 135 patients of the 500 showed stronger skin test reactions than they did to kochia.

An interesting observation made here during the severe drouth of the summer of 1954 is the fact that the summer blooming lamb's-quarters, along with the regular lamb's-quarters, was able to survive the drouth much better than did the ragweeds. This in itself may have some scientific value in establishing this weed as a factor in inhalant allergy.

No definite conclusion could be made as to this plant's being the chief causative factor in inhalant allergies of the summer months because of the abundance of other inhalants in this area during these months; however, this plant did produce stronger skin test reactions in a certain per cent of sufferers than did the common offenders during this time of year.

The mucous membrane test was done on some patients who showed a positive skin reaction. A large majority of these patients showed lacrimation and injection of the conjunctiva, sneezing, rhinorrhea, and general hay fever symptoms. Of this group, summer blooming lamb's-quarters hyposensitization was begun, along with other incriminated inhalants, and good results were obtained.

SUMMARY

Five hundred private patients were skin-tested intradermally with an allergenic extract 1:1000 solution of summer blooming lamb's-quarters *(Chenopodium paganum Reichenb)* and the result was compared with skin tests of pollen of grasses and weeds pollinating in this area during the summer months and the results recorded and tabulated.

An effort was made to single out those patients who had sensitization to the more common weeds, grasses, and inhalants of the area, and to see how they reacted to the summer blooming lamb's-quarters.

CONCLUSIONS

This investigation seems to indicate that this weed is a causative factor in inhalant allergy in the summer months. This early pollinating goosefoot weed, summer blooming lamb's-quarters *(Chenopodium paganum Reichenb)*, should therefore be suspected and tested for in those patients who have inhalant allergies in the early summer months, particularly those who have not responded to hyposensitization with amaranthus, grasses, molds, and other summer inhalants. It should also be kept in mind as an aggravating factor in later summer and fall pollinosis.

506 Hales Building

A CLINICAL COMPARISON OF CARBINOXAMINE MALEATE, TRIPELENNAMINE HYDROCHLORIDE, AND BROMODIPHENHYDRAMINE HYDROCHLORIDE IN TREATING ALLERGIC SYMPTOMS

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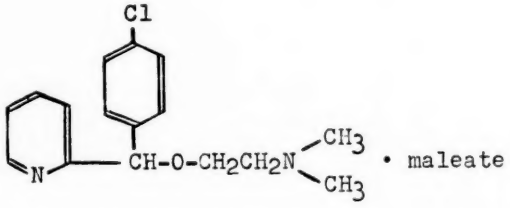
SINCE the introduction of specific histamine antagonists by Bovet and Staub in 1937,[1] and Halpern in 1942,[4] the search for better compounds has gone on steadily. As in the case of other classes of useful drugs, the object has been to find new forms that show greater specific effectiveness, and that have less toxicity or fewer undesirable side effects.

Presently available antihistamines are reasonably efficient in counteracting histamine, and are widely used in treating allergic symptoms other than asthma. Excellent review on these drugs have been prepared by Brown and Krabek,[2] and Feinberg,[3] so it is not necessary to discuss here in detail the properties of the many compounds in accepted use.

However, it is not easy to get complete relief of symptoms with antihistamines,[3] and the numerous side effects, particularly somnolence, impair their usefulness in many patients. The new antihistamine, Clistin® Maleate (Carbinoxamine Maleate, McNeil) has been developed with the aim of overcoming these objections. This preparation is 2-[p-chloro-α-(2 dimethylaminoethoxybenzyl)] pyridine maleate, and has the following chemical structure:



Physically, it is a white water soluble powder. It is almost tasteless and has very little local anesthetic property, unlike many other antihistamines. Given orally it is a potent agent in preventing fatal histamine bronchospasm in guinea pigs and has a very high ratio of lethal to antihistamine

Dr. MacLaren is an Associate Fellow of the American College of Allergists.

From the Department of Medicine (Allergy) of the University of Southern California, School of Medicine, and the Allergy Clinics, Los Angeles County Hospital. The study was made possible through the co-operation of James M. Shaffer, M.D., McNeil Laboratories, Inc., Philadelphia, Pa. The Ambodryl hydrochloride was supplied through the kindness of Parke, Davis and Co., Detroit, Michigan.

TABLE I. CHARACTERISTICS OF SEVENTY PATIENTS TREATED WITH CLISTIN MALEATE, AMBODRYL HYDROCHLORIDE AND PYRIBENZAMINE HYDROCHLORIDE

Disease	No. Cases
Allergic rhinitis	41
Allergic rhinitis and asthma	26
Allergic rhinitis and eczema	3
Total all cases	70

AGE DISTRIBUTION

Decade	No. Cases
1-10	16
11-20	10
21-30	11
31-40	13
41-50	8
51-60	11
Over 61	1
Total	70

There were 30 males and 40 females

dose (2740/1).[6] It is claimed to control allergic symptoms in small (4 mg) doses, and to show minimal side effects.

The purpose of this report is to compare in clinical effectiveness this antihistamine with two previously established antihistaminic compounds, Ambodryl® (bromodiphenhydramine hydrochloride, Parke, Davis) and Pyribenzamine® (tripelennamine hydrochloride, Ciba). To reduce the subjective factor, a control placebo exactly resembling carbinoxamine maleate was used.

MATERIALS AND METHODS

The daily doses of the drugs administered to the subjects of this study were: carbinoxamine maleate 4 mg, bromodiphenhydramine hydrochloride 25 mg, tripelennamine hydrochloride 50 mg, and the placebo, one tablet, each three times a day. Occasionally, larger or smaller doses were prescribed if the subjects' tolerance varied greatly from the normal.

The drugs were started in random order, and the schedules arranged so that any one time each drug was being used by one-fourth of the subjects. In this way variations in symptoms due to weather, season, or other common external factors tended to cancel out. At the end of a specific period, of one or two weeks, each subject was shifted to another drug, until all had rotated through the four.

Data in regard to diagnosis, age, and sex of the patients co-operating in this study are given in Table I. These seventy patients fell into three groups. The first group of thirty-six patients was drawn from the Allergy Clinic at the Los Angeles County Hospital. These subjects used each of the three drugs and the placebo for two consecutive weeks, which required eight weeks to complete the cycle. During the time they were taking part in the study, other medication was withheld, and if any were taking desensitization injections these were also stopped.

TABLE II. AVERAGE SYMPTOM UNITS PER WEEK OF 46 PATIENTS WITH ALLERGIC RHINITIS TREATED WITH ANTIHISTAMINES AND PLACEBO

Drug	Symptom Units/Week
1. Pyribenzamine	21.2
2. Clistin	22.7
3. Ambodryl	24.0
4. Placebo	28.0

The second group consisted of ten patients from private practice, each of whom rotated through the three drugs and the placebo, spending one week on each. The shorter period was used here because of the difficulty of keeping these subjects on medication that was not as effective as that to which they were accustomed, or which produced uncomfortable side effects.

Groups one and two, consisting of forty-six patients, will be treated together, since the same method of scoring clinical relief was used in each. In this method of scoring, which has been used before by us in evaluating drugs,[5] the patient is given each week a sheet listing symptoms down one side and provided with spaces in which the number of symptoms each day can be tallied. For example, "attacks of coughing," "sneezing spells," "attacks of wheezing," "running nose," and "itching eyes" can be counted each day in the proper column. In addition, the actual number of antihistamine pills taken, the amount of supplemental medication used, and the various appropriate remarks are put down on the score sheet.

At the end of the week the investigators totaled the number of symptoms (called symptom units) in each category, recorded side effects as elicited by questioning, and put down the patients' estimate of degree of relief. The objective or "actual" degree of relief, which did not always coincide with the patients' opinion, was calculated from the average number of total symptom units per week for each drug. Thus a fit of sneezing morning and night counted as two symptom units for that day; if, in addition, there was rhinorrhea twice that day, the total for the day would be four units. Each drug could be assigned a numerical figure of merit in this way.

Group three consisted of twenty-four cases from private practice, who were treated with each drug and placebo for two weeks in turn, just as were the patients in Group one. However, these patients did not keep daily records of symptoms, but reported each week on the degree of subjective relief experienced, and on any side effects noticed.

RESULTS

In Table II are summarized the results in terms of symptom units per week, as found in the forty-six cases of groups one and two, based on a total of 424 weeks of treatment. The best "score," namely, the lowest average symptom count per week, was shown by tripelennamine, with the value of 21.2 symptom units. This was followed closely by carbinoxamine

maleate, with 22.7, and bromodiphenhydramine hydrochloride with 24.0. The control value with the placebo was 28.0.

By adding the values assigned to the degree of subjective relief (none = 0, slight = 1, moderate = 2, marked = 3, complete = 4) for all seventy cases in the study, the figures shown in Table III are derived.

TABLE III. SUBJECTIVE RELIEF SCORES OF 70 PATIENTS TREATED WITH ANTIHISTAMINES AND PLACEBO

Drug	Subjective Relief Score
1. Pyribenzamine	160
2. Ambodryl	146
3. Clistin	137
4. Placebo	85

Again, tripelennamine had the best "score," at 160. Bromodiphenhydramine was second by this method of measuring relief, with the figure 146, and carbinoxamine maleate third with 137. The placebo was last, with a count of 85.

The number of cases experiencing side effects and the approximate severity thereof are shown in Table IV. Sedation was estimated as follows: 1 plus, if spontaneously noticed by the patient but causing no difficulty; 2 plus, if conscious effort was required to keep fully alert; and 3 plus, if effort was necessary to keep awake.

TABLE IV. NUMBER OF PATIENTS IN GROUP OF SEVENTY SHOWING SIDE EFFECTS FROM TREATMENT WITH ANTIHISTAMINES AND A PLACEBO

Side Effect	Pyribenzamine		Clistin		Ambodryl		Placebo	
	No.	Percent	No.	Percent	No.	Percent	No.	Percent
Sedation one plus	14	20.	8	11.4	12	17.2	0	
Sedation two plus	5	7.1	1	1.4	8	11.4	1	1.4
Sedation three plus	4	5.7	2	2.9	2	2.9	0	
(Total Sedation)	(23)	(32.8)	(11)	(15.7)	(22)	(31.5)	(1)	(1.4)
Dizziness	4	5.7	1	1.4	2	2.9	2	2.9
G. I. distress	4	5.7	3	4.3	4	5.7	3	4.3
Headache	1	1.4	3	4.3	3	4.3	0	
Dryness mouth or nose	1	1.4	0		0		0	
Total all complaints	33	47%	18	25.7%	31	44.4%	6	8.6%

Carbinoxamine maleate produced the fewest complaints of drowsiness, as well as the lowest incidence of all side effects of the three antihistamines. The eighteen complaints from it were a little more than half the thirty-three from tripelennamine or the thirty-one from bromodiphenhydramine. In general, it was noted that if a patient was made drowsy by one antihistamine, the others tended to have the same kind of effect. Just as the placebo showed activity in relieving symptoms of allergy, so it produced complaints of side effects in six instances.

DISCUSSION

Evaluation of a drug that does not have an "all or none" effect, or a clear cut end point can produce only an approximate rather than an exact

answer. The larger the series, the fewer the variables and the more rigorous the statistical analysis, the closer the approximation comes to an exact figure. For clinical purposes, however, data somewhat short of mathematical exactitude serve adequately.

In this study we have chosen to make a serviceable evaluation of a new antihistamine by comparing it with two others on which previous experience has been gathered.[2,7] Since each drug, as well as a placebo, was submitted to the same process, the variables are presumably nearly equal and the relative effectiveness of the drugs should be reliably determined. We have tried to reduce the subjective element in measuring relief of symptoms by a daily record, rather than trusting entirely to the patient's impression expressed after a period of trial.

Our results show that none of the antihistamines used in recommended doses produced complete relief of nasal allergy, except in a few cases. If any had abolished symptoms completely in all cases in which it was tried, the "average symptom units" for that drug shown in Table II would have been zero. This difficulty in suppressing symptoms completely has been commented on by Feinberg,[3] and indicates that further work on new compounds is desirable.

In terms of "average symptom units" the spread between the three antihistamines is not great, which makes it appear that they are closely comparable in effect. Assuming that the figure for the placebo represents the untreated state, the antihistamines reduced symptoms on the average by the following amounts: tripelennamine hydrochloride 24.3 per cent, carbinoxamine maleate 18.9 per cent, and bromodiphenhydramine hydrochloride 14.3 per cent. These figures should be accepted with caution, since there is good evidence that the placebo alone has a definite effect in reducing symptoms in a certain percentage of patients. Therefore, the period on placebo may not represent the true picture of untreated allergy.

The data on the patients' own estimate of relief shows the best score for tripelennamine hydrochloride, followed by bromodiphenhydramine hydrochloride, and carbinoxamine maleate. Again, had any of the drugs consistently produced subjective relief of symptoms, its score would have been 280 (70 patients $\times$ 4). It is of some interest to note that the order of subjective relief is the same as the frequency of producing somnolence. The sedative effect may make patients feel better than their symptom count indicates them to be.

Side effects except for gastrointestinal distress and headache were much less with carbinoxamine maleate than with the other two antihistamines. Somnolence in particular was encountered only half as often. This suggests that larger doses than the 4 mg originally recommended could be used. We would expect greater control of symptoms without raising the side effects beyond an acceptable level.

SUMMARY

1. Three antihistamines, Clistin Maleate (carbinoxamine maleate), Pyribenzamine Hydrochloride (tripelennamine hydrochloride), and Ambodryl (bromodiphenhydramine hydrochloride), together with a placebo, were compared on seventy patients for their respective ability to relieve allergic nasal symptoms.

2. The amounts by which actual symptoms were reduced were, respectively, tripelennamine hydrochloride 24.3 per cent, carbinoxamine maleate 18.9 per cent, and bromodiphenhydramine hydrochloride 14.3 per cent.

3. With respect to subjective relief as reported by patients, the order of effectiveness was tripelennamine hydrochloride, bromodiphenhydramine, and carbinoxamine maleate.

4. The most prominent side effect of each drug was somnolence. In this respect carbinoxamine maleate produced only half as many complaints as the other two.

5. The placebo produced both subjective and objective relief in certain patients.

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WR 1339 INHALATIONS IN THE TREATMENT OF ASTHMATIC ATTACKS AND CHRONIC ASTHMA—A PILOT STUDY

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THE tenacious viscid mucous and mucopurulent exudate found in the bronchial tree of many asthmatic patients, acting to produce partial obstruction has been an ever-present factor in the pathologic physiology of the patient with asthma, and, clinically, a difficult problem to solve. For the presence of this obstructive exudate, clinically, helps to initiate severe coughing, wheezing and dyspnea, symptoms usually not relieved until this material is partially or completely ejected by coughing. Attempts to liquefy these secretions by use of medicinals, such as potassium iodide, ammonium chloride and other drugs, seem centuries old. Unfortunately, as many asthmatic patients can attest, these drugs have not been universally successful.

J. B. Miller has been a pioneer in the search for a new method of liquefying these exudates. He investigated an alkylaryl poly-ether alcohol, known as Triton A-29 or Alevaire,® (WR 1339) and its effect on the liquefaction of the exudate in tuberculous patients.[4,2,5] This preparation is a "detergent, chemically inert, stable in the presence of strong acids and alkalies, unaffected by boiling or prolonged standing and compatible in solution with antibiotics, buffer salts and a wide variety of medicinals."[6] Tissue lipases do not digest it[3] as with many other synthetic detergents and it retains its detergency in the tissues for a very long time. Its physical activity in lowering surface tension renders it a useful agent, medically, for the lowering of surface tension of these exudates and secretions and neutralizes their forces of inner cohesiveness, thereby making them less viscous and coughed up more easily. This useful detergent is, fortunately, apparently non-toxic[7] having been used in a culture medium for growing bacteria[1] and having been inhaled in 50 per cent concentration for long periods of time without pathologic changes in experimental animals.[6]

Miller and associates have investigated the clinical usefulness of this mucolytic detergent in a wide variety of respiratory conditions in children[5,8] and adults.[9] The author undertook a preliminary study in June 1953 to determine specifically what the effects of its inhalations on asthmatic patients, with and without such complications as emphysema, might be.

PROCEDURE

Since this was a preliminary study, it seemed important to choose patients in an actual attack of asthma with characteristic dyspnea. These

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WR 1339 is the laboratory designation for Alevaire® (Winthrop-Stearns). Read by title at the Eleventh Annual Congress of the American College of Allergists, April 28-30, 1955, at Chicago, Illinois.

were treated with WR1339 using a simplified office technique. Oxygen at 6 liters flow per minute was passed through a plastic nebulizer containing 2 cc of 0.125 per cent Alevaire. The other end of the nebulizer was connected up to a BLB face mask through which the patient inhaled the detergent for fifteen minutes, by which time most of the solution would have been completely nebulized. A timer was placed next to the patient who was told to note how soon he first felt some significant relief, and then to compare this to the additional relief felt at the end of fifteen minutes, if any. If relief was obtained, the patient, was asked after the treatment, to record for how long such relief was maintained.

After early studies revealed, surprisingly, that from a single treatment, relief often lasted for five days or longer, it was decided to try a number of asthmatics on this nebulized mucolytic detergent several times per week, usually two or three times a week, but in one instance five times a week, to determine if, thereby, the patient could be kept relatively symptom free. A careful notation was made of the quality and quantity of symptomatic medication being used by each patient. The patient was asked to give up as much of the symptomatic medication as he could, if and when he obtained sufficient relief from the inhalations. A notation was made of the amount by which medications was reduced. In several patients in whom substantial relief was obtained during one or two months of inhalations, they were deliberately stopped in order to determine how long the benefits might last.

All of the individuals used in this phase of the study were asthmatic patients who were inadequately controlled by desensitization therapy and/or symptomatic medication. Thirteen of the twenty-two patients had a complicated emphysema, and one had a bronchiectasis.

RESULTS

In Asthmatic Attacks.—Ten patients with asthma were given WR 1339 aerosol inhalations during an acute asthmatic attack. Two of the ten obtained 100 per cent relief; one of these had emphysema and one had bronchiectasis. One also with emphysema obtained 75 per cent relief. Two others, one a girl, age ten, with emphysema, obtained 50 per cent relief. Five patients, three of whom had marked emphysema and one a mild emphysema, obtained absolutely no relief, in fact two had their dyspnea aggravated.

In Chronic Asthma.—Fourteen patients were treated with these aerosol inhalations, one to three times weekly, and in one patient with a myocarditis also, for a while five times weekly, for periods ranging from one to four months. Compared to the number and severity of the previous asthmatic attacks, the interim state between severe attacks and the amount of previously necessary symptomatic medication the patient could give up, WR 1339 inhalations appeared to be responsible for 100 per cent relief

TABLE I. ALEVAIRE INHALATIONS IN ACUTE ASTHMA

Case	Sex	Age	Duration Asthma	Alevaire	
				No. of Treatments	Results
1. G.H.	M	71	*Emphysema 22 years	1, during attack	0%. No relief.
2. J.S.	M	64	*Emphysema 9 years	4, during attacks	100% relief in 5′ to 10′. Lasts 3-5 days.
3. R.H.	F	60	*Emphysema 27 years	1, during attack	75% partial in 7′, Mod. in 15′.
4. S.W.	M	58	*Emphysema 20 years	2, during attack	0%. No relief.
5. A.P.	M	35	17 years	1, during attack	50% partial relief in 15′.
6. T.L.	M	55	*Bronchiectasis 25 years	Started 6/22/53 10, during attacks	100% relief in 5-15′. Lasted 2-24 hours.
7. G.L.	F	38	*Emphysema 35 years	1, during attack	0%. Made her worse.
8. C.K.	F	55	*Emphysema 2 years	5, during daily attacks	0%. No relief.
9. M.C.	F	50	3 years	3, Few hours before nightly attacks	0%. Did not prevent nightly attacks.
10. D.F.	F	10	*Emphysema 10 years	1, during attack	50% Partial relief by 15′.

*Complication in addition to asthma.

in one of the fourteen cases, 80 per cent relief in nine cases and 50 per cent relief in four cases. There were no complete failures in the fourteen treated on the chronic basis. Six of the twelve cases with over 80 per cent relief gave up the use of all symptomatic medication. Six of the 80 per cent relief cases gave up most of their medication. In the two 50 per cent relief cases, medication was reduced by 50 per cent in one case and 75 per cent in the other. Six of the fourteen patients had emphysema in addition to asthma. Tables I and II illustrate the results in more detail.

Since this was a pilot experiment, no studied effort to run a series of controls was attempted.

DISCUSSION

Miller and his associates[9] have reported on the treatment of eleven chronic asthmatic patients with WR 1339 inhalations. They obtained good results in all but one case. It is interesting and important to note, however, that their manner of treatment differed from the one herein reported in two respects. They used an open tent on some patients and nasal tips in others, both attached to nebulizers and air compressors equal to an oxygen flow of 8 to 10 liters per minute. These techniques offer greater advantage for home therapy and prolonged therapy. And from the point of view of time, each treatment they gave lasted from an hour to days on a continuous basis, compared to the fifteen minutes, two to three times weekly used in the present study. Aware of the change in viscosity effected by this surface acting detergent, one cannot help feeling that the more prolonged each treatment and the more frequent the treatments, the greater the potentialities for reducing viscid exudates or plugs in bronchi into thin easily evacuated secretions.

Miller's case reports are extremely interesting and bear some analysis. He reports on one man who, after suffering from asthma for fourteen years, was treated with WR 1339 once daily for an hour, and who in two weeks was completely asymptomatic and has remained so since December, 1953. In essence, most of his patients lost their sputum after

TABLE II. ALEVAIRE INHALATIONS IN CHRONIC ASTHMA

Case	Sex	Age	Duration Asthma	Severity of Recent Asthma			Drugs Recently Used	Alevaire	
				Dyspnea	Wheeze	Cough		Date Started and No. Treatments	Results
1. DL	F	33	10 yrs.	Daily and slight but status for week before Alevaire			KI—tid, Amminoph—qid Penicillin inj.	10/23/53 2x/wk 16 in 6 wk.	Slight wheeze and dyspnea 2-3x/wk. Discontinued all Drugs. 80% relief.
2. JS	M	64	Emphysema 9 yrs.	10x/day	10x/day	10x/day	KI—bid 10 Norisedrine Inhalor—day	9/8/53 1x/wk. 4 in 1 mo.	Relief lasts 3-5 days. Gave up KI. Reduced Inhalor to 2-3x/day. 50% relief.
3. EV	F	57	7 yrs.	Since on desensitization attacks reduced to 1 daily.			Tedral 1/day KI—tid Amminoph—tid	10/23/53 2x/wk. 26 in 3/mos.	Only 6 attacks in 3 mos. used 6 Tedral. Continued KI and Amminoph. 80% relief.
4. JG	M	72	Emphysema and Myocarditis. 12 yrs.	Continuous wheeze and dyspnea, esp. with slight effort.			KI—tid Tedral—qid Amminoph—tid	11/26/53 3x/wk. 1/wk.—5x 30 in 2 mos.	Gradually lost wheeze and dyspnea except on effort. Reduced Tedral and Amminoph by 50%.
5. TL	M	55	Bronchiectasis 25 yrs.	If bad has it off and on for days. Spasmodic with cough.			None	6/22/53 2x/wk. 16 in 2 mos.	Reduced frequency of attacks markedly. 80-90% relief.
6. DS	F	43	Emphysema 25 yrs.	Mild asthma daily despite desensitization.			Tedral—bid KI—tid Amminoph—bid	7/23/53 2x/wk. 25 in 4 mos.	After 2½ mos. lost all asthma. No KI or Tedral. Amminoph 1/day. 80% relief.
7. BC	F	46	4 yrs.	6x/day	6x/day	6x/day	KI—tid	11/6/53 3x/wk.	After 2 wks. complete relief. Lasted 4 wks. no drugs. 100% relief.
8. EJ	M	38	8 yrs.	Prompt relief from Norisedrine inhaler. 4x/day	4x/day	4x/day	Amminoph—qid KI—tid PBZ—qid Tedral—bid Butaneph Inj—bid	12 in 1 mo. 11/13/53 2x/wk. 17 in 2 mo.	50% relief in intensity and frequency and use of drugs. 50% relief.
9. JH	F	65	14 yrs.	Continuous dyspnea past mo. Attack with cough every 3 a.m.			KI—tid Amminoph—5x/day	11/16/53 1x/wk. 5 in 5 wks.	Only 3 a.m. cough. On amminoph. bid. Lost dyspnea. 80% relief.
10. JA	F	41	6 yrs.	4-5x/day	Continuous past 20 days		KI—bid Amminoph—qid	11/30/53 1-2x/wk. 20 in 3½ mo.	Lost dyspnea; cough and wheeze. 1-2x/day for 5'. Off drugs 90% relief.
11. CL	F	33	20 yrs.	3-4x/day for past 2 mo.	3-4x/day Quit Tedral past mo.	3-4x/day	None past mo.	1/28/54 3x/wk. 26 in 2 mo.	After 5 treatments 3x/wk. lost all symptoms except 5 a.m. wheeze. No drugs, 90% relief.
12. LC	F	36	5 yrs.	Dyspnea on and off thru day and night. Relief with expectoration—temporary.			KI—tid Tedral—bid Amminoph—qid	10/8/54 3x/wk. 12 in 1 mo.	Relief for 1-2 days after treatment. Symptoms milder. Gave up amminoph. Cut Tedral to 1/day. 50% relief.
13. DP	M	65	Emphysema 65 yrs.	3-4x/day Also dyspnea with exertion.	Mild and continuous	3-4x/day	Amminoph—qid KI—tid	3/4/54 1-2x/wk. 48 in 4 mo.	Only 1 attack nightly, wheeze only. Off KI On 1 amminoph/day. 80% relief.
14. CH	M	73	Emphysema 1 yr.	No wheeze; cough and dyspnea on and off with and without effort.			KI—tid	2/8/54 2x/wk. 7 in 1 mo.	Fine relief after 2 treatments. 80% relief. Relapsed when quit.

using this preparation, and with this disappearance obtained complete or almost complete relief. These results contrast sharply with my own, in two respects, bearing in mind our different techniques and length of time of treatments. Very few of my cases who obtained relief were bothered with much sputum and, although they may have had some liquefaction of their secretions consistent with therapy, the liquefaction of sputum did not appear to be a prominent factor in these cases. This might suggest to some that perhaps bronchospasm may also be relieved as a result of these inhalations or, what appears to be more likely, that in many cases of asthma a relatively small amount of mucoid secretion added to a strong bronchospastic element is enough to produce the obstruction which induces the asthmatic attack. Again, whereas Miller's cases seemed to go on for six to eight months or longer with continued relief, mine tended to relapse within a month or two after termination of therapy. In one case kept on inhalation for three months, there was a relapse during therapy.

Theoretically, the elimination of exudates and secretions of an obstructive nature from the bronchial tree is the key to successful relief of asthma. It remains to be seen, however, from further studies in this field whether or not relief obtained by Alevaire inhalations is of a temporary nature perpetuated by continued short repeated treatments or (as the author hopes) can be of a prolonged nature induced by more protracted and intensive therapy. It may be noted from the tables that the author's cases for the most part had a complicating emphysema or were otherwise fairly severe cases of asthma. One certainly would anticipate that more continuous and intensive inhalation therapy as described by Miller might produce more prolonged relief.

At present a more comprehensive study on such inhalations encompassing spirometric studies, is in progress. We hope in this manner to follow objectively the degree of immediate and prolonged relief by whatever technique of administration we may use.

CONCLUSIONS

1. Theoretically, liquefaction of mucoid secretions in asthmatic patients should help the patient to eject the obstructive exudates and relieve the asthmatic state.

2. Surface tension acting detergents, such as Alevaire (WR 1339), seem capable of performing this function.

3. Ten asthmatic patients were treated by inhalations of this product through a nebulizer during an asthmatic attack. Five showed 50 per cent to 100 per cent relief within fifteen minutes, which lasted several hours to days.

4. Fourteen chronic asthmatics were given the inhalations two to three times weekly. All of these patients obtained from 50 per cent to 100 per cent relief; eleven cases obtained 80 per cent relief. Seven of the

patients dispensed with all other medication. The others reduced their symptomatic medications by 50 per cent or more.

5. All patients relapsed within a month after treatment was stopped.

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POSTGRADUATE COURSE IN PEDIATRIC ALLERGY

The Division of Graduate Studies and the Department of Graduate Pediatrics of New York Medical College, Flower and Fifth Avenue Hospitals, announce a postgraduate course in pediatric allergy to be held Wednesdays from 9 a.m. to 4 p.m., from November 2, 1955 to May 31, 1956, under the direction of Bret Ratner, M.D., Professor of Clinical Pediatrics and Associate Professor of Immunology. A fee of $300 will be charged for the course, which will consist of lecture-seminars, laboratory and clinical procedures, clinic work, ward rounds, and animal experimentation covering basic principles of diagnosis and treatment of allergy in children, and applied immunology. Enrollment is limited, and all applicants must be certified in pediatrics or have the requirements for certification. For information and registration apply to the Office of the Dean, New York Medical College, Fifth Avenue at 106th Street, New York 29, New York. A research fellowship in pediatric allergy is available, and application for this should be made at once.

USE OF CHLORPROPHENPYRIDAMINE MALEATE INJECTION IN BLOOD TRANSFUSIONS

Further Observations

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BECAUSE the incidence of allergic and pyrogenic reactions to transfusions of whole blood was found to be reduced by the addition of a solution of the antihistamine chlorprophenpyridamine maleate (Chlor-Trimeton Maleate®) to blood prior to transfusion,[1] this procedure has been continued. The patients in the study of the use of this antihistamine with blood for transfusion now number 1064.

The original report by Frankel and Weidner[1] covered 592 transfusions. Among these, 284 pints of blood were given to which 10 or 20 mg of the antihistamine had been added. The remaining 308 pints were given without the addition of the antihistamine. The incidence of allergic or pyrogenic reactions among the patients receiving blood with antihistamine was 0.3 per cent compared with an incidence of such reactions of 3.5 per cent in the group receiving blood alone.

These results with chlorprophenpyridamine maleate in injectable form agree well with those of other investigators.[2-4] Muñoz Baratta[2] eliminated allergic and pyrogenic reactions to blood transfusion in twenty patients who previously had shown reactions, by adding this antihistamine to blood before transfusion. A reduction in the incidence of allergic and pyrogenic reactions from 6.3 per cent among 350 control patients to 0.6 per cent among 300 patients receiving blood containing 10 mg Chlor-Trimeton Maleate per pint was achieved by Offenkrantz, Margolin, and Jackson.[3] Simon and Eckman[4] reported a 0.21 per cent incidence of such reactions among 987 patients protected by the antihistamine mixed with the blood they received, and a 1.71 per cent incidence among 995 control patients.

PRESENT STUDY

An additional 472 pints of blood (some with added antihistamine in injectable form) have been given since the original 592 transfusions were reported. In the present series 361 pints of blood had chlorprophenpyridamine maleate added and 111 pints were used without antihistamine.

Ten milligrams of the antihistamine in solution for intravenous injection were added to the blood immediately prior to transfusion. The flask containing the blood was brought to the bedside. The contents of a sterile 1 cc ampul containing 10 mg Chlor-Trimeton Maleate* were drawn into a sterile syringe and then injected through the air vent into the flask. The flask was then gently rotated to assure even distribution of the drug.

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*Supplied by the Division of Clinical Research, Schering Corporation, Bloomfield, New Jersey, through the courtesy of George Babcock, Jr., M.D.

Following this, the transfusion was accomplished in the usual manner.

Among the 361 transfusions with added antihistamine, only one reaction occurred, an incidence of 0.3 per cent. This allergic-type reaction occurred in a woman with chronic cirrhosis of the liver and esophageal varices who had previously had numerous blood transfusions. The reaction occurred to type A, Rh positive blood. Subsequently she received on different occasions two pints of type O, Rh positive blood with 10 mg of the antihistamine in injectable solution added, and exhibited no reactions. After a lapse of a few months, a pint of type A, Rh positive blood containing the antihistamine, 10 mg, was again given with no reaction noted.

No side effects attributable to chlorprophenpyridamine maleate could be detected in any of the patients receiving the 361 transfusions of blood with the drug added. No drowsiness or other actions of the type attributable to antihistamines occurred.

Four allergic or pyrogenic reactions occurred on the administation of 111 pints of blood with no added antihistamine, an incidence of 3.6 per cent. These reactions were definitely not caused by mismatching, hemolysis, or agglutination. The blood to which the patients reacted, as is customary in such occurrences, was retyped and again cross matched. Neither the type nor the Rh factor had any causative relationship to the reaction.

SUMMARY

In continuation of a study of the protection against allergic and pyrogenic reactions to blood transfusions afforded by chlorprophenpyridamine maleate in injectable form, 472 additional pints of blood have been transfused, or a total of 1064 in two series. The transfusions reported here, 361 made with 10 mg of the antihistamine added and 111 with no added antihistamine, show a reduction in the incidence of such reactions from 3.6 per cent in the control series to 0.3 per cent in patients protected by antihistamine. Grouping the 592 transfusions of the previous series with the 472 of the present, the incidence of allergic or pyrogenic reactions was 3.6 per cent in the 419 control transfusions and 0.3 per cent in the 645 transfusions of blood to which the antihistamine in solution for injection had been added. The addition of this antihistamine to blood for transfusion is concluded to be a highly satisfactory means of preventing allergic and pyrogenic transfusion reactions.

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PRESIDENTIAL ADDRESS

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ONE year ago, as President of the American College of Allergists, I expressed my deep appreciation for the honor of serving you. At that time, I tried to anticipate the many obligations associated with the conduct of this office. Now I know from experience what the responsibilities of a president are, and with added humility do I thank you again for the opportunity of sharing your great confidence.

In many respects my tasks as president have been made easier by harmonious co-operation of all of my fellow officers. Our Past President and Chairman of the Board of Directors, Dr. M. Murray Peshkin, in particular, has been most patient and understanding in his helpful suggestions and sound advice on the many occasions I have requested his counsel. Through their intimate knowledge of the workings of the College, our Secretary-Treasurer, Dr. Fred W. Wittich, and our Executive Vice-President and Counsel, Mr. Eloi Bauers, have handled routine administrative problems in their customarily efficient manner. My successor, Dr. Lawrence J. Halpin, whom you have so wisely chosen to direct the College for the ensuing year, has been a great inspiration to me. You may have every confidence concerning the direction of the College under Dr. Halpin's leadership.

Before discussing other matters pertaining to the College, let me pay tribute to the Women's Auxiliary of the American College of Allergists. The Auxiliary marks its first anniversary at this meeting with appropriate completion of its organizational duties. On behalf of the College, let me express to the officers and members of the Auxiliary our very best wishes for the continued success of their endeavors. We are proud that they have created such a unique society, because we know that all their efforts are directed ultimately in our behalf.

As members of the College we should derive much personal satisfaction from the fact that with each succeeding year our organization functions more smoothly. This wholesome situation is a sign of our increasing maturity and reflects particularly the modifications and streamlining of our by-laws during recent years. These innovations make it easy to effect a better adaptation to actual needs and changing circumstances. As a result of redefinition of specific duties, your Board of Directors for the past two years has held interim meetings, at which many of the policies of the College have been formulated for subsequent consideration by the Board of Regents. Contrary to the expressed fears of some that this activity by the Board of Directors might usurp the authority of the Board of Regents,

Delivered at the Eleventh Annual Congress of the American College of Allergists, April 29, 1955, at Chicago, Illinois.

the real governing body of the College, nothing of the sort has happened. Recommendations by the directors are in no way binding on the regents, but in many instances the directors have served essentially to crystallize controversial issues so that decisions by the regents could be made on the basis of more complete knowledge of the questions involved. With such assistance from the directors, the Board of Regents is now able to function more deliberately and efficiently.

The activation of an experienced and seasoned finance committee of three ex-presidents should be particularly helpful in realistic budgetary decisions. This year the Board of Regents placed your President-elect, Dr. Halpin, in over-all charge of the program for the annual meeting for his better orientation regarding special problems confronting the College, if indeed he needed any such review.

Under the able direction of Dr. Giles Koelsche, the college component of the joint College and Academy Committee for Certification in Allergy has labored earnestly, and at times it appeared hopelessly, for a separate board in allergy. Without encroaching upon Dr. Koelsche's report, which he will give at length, I wish to emphasize some of the broader aspects of certification in allergy which to me is the most serious problem confronting allergists today.

Before I proceed, let me mention a few features of the practice of allergy about which we as allergists have no controversy. In the first place, the phenomena of hypersensitiveness may involve all tissues of the body and consequently must be considered in every field of practice, be it otolaryngology, dermatology, gastroenterology, neurology, hematology, or even surgery as well as internal medicine, geriatrics and pediatrics. Furthermore adequate specific allergy diagnosis and therapy, as well as rational procedures for symptomatic relief, require specialized, intensive training and experience which cannot be acquired in any sort of sideline endeavor. In spite of these undebatable facts, certification in allergy within the framework of the Advisory Board for Medical Specialties can be obtained now only on a subcertification basis, and only after primary certification in either medicine or pediatrics.

This illogical and paradoxical situation is doubtless largely responsible for the failure of the specialty of allergy to attract more young physicians in recent years. Although our growing population is becoming more allergic by virtue of improved transportation facilities and exposure to an increasing number of more complex sensitizing agents, there is only one allergist for each 10,000, or one certified allergist for 75,000 allergic persons in this country! Unless this bottleneck is broken, more and more allergic patients will be treated by physicians inadequately trained in allergy, with emphasis on symptomatic relief measures only, and disregard for specific manipulations. Is it possible that we have already witnessed the highest development of the science of specific allergy diagnoses and treatment, based on fundamental immunologic concepts?

Dr. Koelsche might tell you of some of the thinking of the members of the American Board of Internal Medicine and the American Board of Pediatrics. It is my personal feeling that, if the American Board of Pediatrics relinquished its subcertification privileges, the way would now be cleared for the establishment of a separate board in allergy.

A logical explanation for the position the American Board of Pediatrics is to me, an allergist, not readily forthcoming. Mature reflection leads me to suspect that the fundamental reason for this impassé is a misunderstanding between the allergists, who would have a separate board, and the pediatricians, who would give up a sub-board.

I do not propose to discuss the many reasons why some pediatricians might desire to maintain certification in allergy on its present basis. It would seem to me that there is one fundamental question to be considered: Is the physician practicing both pediatrics and allergy primarily a pediatrician or primarily an allergist? If he is primarily a pediatrician, as his practice increases he will doubtless devote more of his attention to general pediatric problems and concern himself less with allergy. Several outstanding specialists in allergy who limit their work largely or exclusively to pediatric patients have apparently varied their practice in the reverse direction. In discussing the relative importance of their interests, some of this group have indicated to me that they prefer to be known primarily as allergists.

Diverging points of view in this controversy must be reconciled if we are to make progress. If we continue subcertification in allergy with primary emphasis on any other field of practice, I fear for the ultimate survival of the practice of allergy as a specialty.

In spite of repeated rejections from the Advisory Board for Medical Specialties, the joint committee has after seven years made notable progress in some respects, and now has the unanimous support of the subspecialty group of the Board of Internal Medicine. At its annual meeting recently, the American Academy of Allergy reaffirmed its confidence in the joint committee on certification under the able and untiring chairmanship of Dr. George Piness, and instructed its representatives to continue their efforts toward the establishment of a separate board in allergy within the framework of the Advisory Board for Medical Specialties. I earnestly and unhesitatingly recommend to you that at our business meeting we reward the college component of this joint committee with a similar vote of our confidence. Our cause is just, and with right on our side, we will secure for the practice of allergy an American Board of Allergy.

898 Caroline Street

Editorial

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

POLIOMYELITIS AND ALLERGY

In this issue, a paper by Lubens focuses attention on the relationship of allergic injury in the nasopharyngeal area to the frequency of poliomyelitis during epidemics. Lubens[3] has found that we must not only consider the effect of traumatic disturbances, such as tonsillectomy, as a factor in altering the susceptibility to bulbar polio, but that we must also consider trauma of a more subtle type—the subtle traumatic tissue changes of the inflammatory processes of allergy of the respiratory tract. In Lubens' total of 300 cases in the poliomyelitis epidemic of 1949 and 1950, 150 cases had some manifestation of an allergic condition. Thirty-nine of these people with allergic responses had bulbar poliomyelitis. This was higher than the anticipated rate judging by the population which was not allergic.

If we take the data in Table I in Lubens' paper and calculate chance occurrence of bulbar poliomyelitis in his allergy series, this number would have been 18.8 bulbar cases contrasted with twenty-six cases of bulbar poliomyelitis observed. Non-bulbar cases would have risen to 88.2. In contrast, the randomly expected bulbar cases in the non-allergy series would be 17.2 instead of ten. If these concepts are put into table form, we can more readily visualize the situation.

TABLE A—DATA OF LUBENS

Observed Poliomyelitis in	Non-Bulbar	Bulbar	Total
Allergy Cases	81	26	107
Non-Allergy Cases	88	10	98
	169	36	205

If we wish to determine what would be the ratio of bulbar to non-bulbar cases:

$$\frac{\text{Total Allergy}}{\text{Total Cases}} \times \text{Total Bulbar} = \frac{107}{205} \times 36 = 18.8 \text{ bulbar cases by random occurrence}$$

By similar calculations, the differences between observed cases and cases occurring by chance would be:

TABLE B

	Non-Bulbar	Bulbar
Allergy	−7.2	+7.2
Non-Allergy	+7.2	−7.2

Calculation of Chi² by conventional means shows that the increased frequency of bulbar poliomyelitis in allergy is most probably not due to chance but is significant at the .01 level. If the small number of cases is considered, we may say that there is only one chance in fifty that the data are not statistically significant.

Holbert[2] of Santa Cruz, California, has recently pointed out that of 100 patients with severe residuals of poliomyelitis, all of whom depended upon mechanical respiratory aid for various periods of the day, 62 per cent had one or more of the usual allergic manifestations, such as asthma, hay fever, eczema, stuffed nose, hives, and migraine, with 31 per cent having asthma, eczema, or hay fever.

What happens to allergic patients who are being treated by allergists? Is the anticipated rate of polio increased in this group? Is bulbar polio more frequent? Abramson[1] conducted a survey among 800 allergists, members of national allergy societies in the United States, who gave him data on 153,749 allergic patients under treatment. Only twenty-nine cases of poliomyelitis were reported. The frequency of bulbar paralysis in this group was low. In this group of *treated* allergic patients, only the anticipated rate of poliomyelitis was encountered.

The foregoing discussion and preliminary data merit immediate consideration by the national allergy societies. A survey planned by a joint committee may be needed. Certainly, we must determine whether Lubens' and Holbert's observations can be amplified and thereby confirmed. In view of the normal incidence of poliomyelitis in the treated persons in cases reported by Abramson, it is imperative that, until the questions raised here have been solved, allergic individuals be given the proper therapy, especially immunologic therapy, in areas where poliomyelitis occurs. Dependence upon cortisone should be kept at a minimum, with major emphasis on pharmacologic and immunologic techniques. The anti-inflammatory effects of cortisone and its derivatives, coupled with the fact that cortisone in many species leads to the spread of infections, including infection by viruses, lends more than the usual weight to the need for suitable immunologic, pharmacologic and psychologic control of the neurovascular system that responds by allergic inflammation.

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Progress in Allergy

MISCELLANEOUS REVIEW OF ALLERGY 1954

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This reviewer would like to apologize to those authors whose works are not included in the following paragraphs. Many worthwhile reports were omitted because they were too limited in their scope to be considered as strictly "miscellaneous." For clarity and ease of reference, subjects have been classified as follows: general interest, respiratory, drug sensitivity, dermatology, gastrointestinal, and headache. Though such listing may appear to duplicate the work of other reviewers in this series, an attempt has been made to include that material of unusual or outstanding attraction.

GENERAL SECTION

Education

To the majority of practicing physicians, the work of the statistician is often bewildering and foreboding. Bancroft[8] points out that the statistician may be of considerable help to the allergist, and at the same time the allergist may help himself by an understanding of some of the simpler but important statistical concepts. She states that the primary goal in controlled studies is to make sure that there are at least two groups. The variable under consideration, usually treatment, should be the only differentiating point between these two groups. It is also necessary to determine whether the difference between these two groups is sufficiently large to have any practical significance. As an illustration, Bancroft points out that the cure rate with drug *A* may be 4 per cent as compared with a 2 per cent cure rate with placebo. Although 4 per cent is double of 2 per cent, it must be remembered that perhaps 96 per cent were not cured with drug *A* as compared with 98 per cent with the placebo. Therefore, this difference is not statistically striking. The statistician therefore can help the allergist in the definition of his problem and in the actual setup of the experiment. This includes the plan for assignment of patients to groups and in the assistance supplied by the formation of records facilitating analysis.

There is much that needs to be known about the subject of allergy. There are many fallacies that have lived too long. Black[14] destroys one old fallacy in his statement that the incidence of tuberculosis is no greater among patients with asthma than among nonasthmatic patients. He does not hold with the belief that asthma in a child makes the patient more likely to contract tuberculosis. Peshkin,[114] in his presidential address before the American College of Allergists in 1954, called the medical profession to task for the haphazard and inadequate manner in which allergy is taught in most medical schools. It is the direct responsibility of the allergy specialists to provide more and improved care of the allergic population. Rappaport,[122] complimented both the Academy and the Col-

lege upon the co-operation they had shown in the establishment of the American Foundation for Allergic Diseases. It is necessary to impress the public with the seriousness of allergy as a distressing and important illness. Once this has been accomplished, the public may be approached for financial and moral support for this foundation. Rappaport reported that from 1946 through 1951 allergic diseases ranked twenty-sixth in a list of twenty-nine which received research support from government and private sources. Total expenditures for allergy amounted to $800,000 as compared with $27,000,000 for cancer. This disparity may be one reason why skilled investigators are going into specialties other than allergy. The workings of this American Foundation for Allergic Diseases will bring rich rewards to the field of allergy and to the men interested in this specialty.

The allergist must have an empathetic attitude towards the suffering or discomfort of the patient, in the opinion of Harris.[70] In addition to a history, physical examination, laboratory and sensitivity tests, the allergist must present kindness and thoughtfulness in the care of his patients. This is especially true in this particular field because the patient visiting the allergist is usually a hypersensitive one. The subject of allergy is so broad that no unitarian hypothesis may cover the present knowledge of the disease or, for that matter, of most allergy in general. He brings out the fact that tests with allergenic substances, though important they may be, should not be the sole criterion of clinical sensitivity.

The advantages of a simple graphic drawing representing a survey of the sequence of allergic events in the patient's life is the work of Gutmann.[64] A simple graphic demonstration immediately shows the severity, intensity or seriousness of the allergic complaints.

Siegal and Seideman[139] focus attention upon the state of latent or subclinical atopy. They attempt to determine more precisely the true incidence of hypersensitivity. In 6.6 per cent of 227 persons, latent or subclinical phases of atopy were indicated by reactions to intracutaneous testing. In these persons there were no past or present allergy symptoms. Their studies show the true incidence of atopy in the general population to be about 20 per cent, two-thirds being in the clinical phase and one-third in the latent phase. Of particular interest were the negative passive transfer reactions in four or five subjects with latent atopy. Though these patients showed four plus positive on direct skin test, negative passive transfer reactions were subsequently observed.

The chief qualifications for good allergy is that one should be a good physician. He should be willing to admit his failures to his colleagues. Bowen[17] has termed this the "Achilles heel in allergy." Of the various drugs used for the relief of asthmatic symptoms, this author feels that epinephrine hydrochloride is the best friend the allergist can identify. He cautions against the indiscriminate use of penicillin in the allergic patient with the expression that a more conservative attitude will prevent some of the terrific after-effects of antibiotic therapy. Bowen is of the impression that three-day postgraduate courses have caused a retarding influence in allergy. No one can practice allergy adequately after only a very short course of instruction and lecture listening.

In a fine panel discussion, Mitchell[112] has classified allergic diseases into two kinds—the ones that are easy and the ones that are difficult. The easy ones are the cases that are logical and understandable. The clinical history gives the clue and skin tests are almost always positive. The problem cases may be due to infection, emotional disturbances and

a variety of other non-evident causes. The prognosis in most allergic disorders is usually excellent where a specific allergen can be demonstrated and subsequently avoided. Swineford[112] has stated that allergy is not the only cause of angioedema and urticaria. Infection, psychogenic factors, physical factors, endocrine influences and undetermined agents were the reported causes in his quotation from another source. Atopic or simple allergic causes were found in 35 per cent of the patients. Sheldon[112] feels that suspected gastrointestinal allergy may be founded upon a good positive family history of allergy, associated allergic manifestations, gastrointestinal symptoms and by means of exclusion. In this same panel the greatest dangers in the use of ACTH and cortisone in allergic diseases were presented. These were found to be the possibility of anaphylactic or severe allergic shock with the administration of ACTH, osteoporosis and vascular accidents. The production of vascular lesions was an additional danger to be considered in the use of these hormones. One of the prominent features of tuberculosis or brucellosis is the allergic factor though not necessarily of the atopic type. The mechanism by which infection produces asthma has never been determined. The use of vaccines is empirical—when a patient is treated with a bacterial antigen, the physician does not know what he is doing. One major objection to the use of autogenous vaccines is recognized. There is not evidence that the chronic, infectious asthmatic patient has exacerbations from the same organism each time. The autogenous vaccine may be incomplete unless one has access to all of the sources of bacteria, both saprophytic and pathogenic. Stock vaccines, if they are to be effective, must be very comprehensive.

We have all had the experience of suggesting that a patient use a medication three or four times daily. That same patient may return later with the admission that he did not follow instructions to the letter. Jenkins[78] found that only four patients of twenty-two subjects were completely faithful to directions given for medication to be used at intervals of three or four times daily. The remaining patients missed about as many doses of medication as they took.

Surface anesthesia may be produced by skin cooling and thus reducing the pain of injections. MacKenzie[101] freezes a colored aqueous solution of Zephiran® in ordinary refrigerator ice trays. This is used to rub the injection site firmly until the skin is well chilled. Then the injection made with a sharp needle is practically painless.

ALLERGY IN CHILDREN

Prevention

Glaser[55] has reported that in 516 allergic patients he noticed recurrent upper respiratory infections on a sensitivity basis in 30 per cent and perennial allergic rhinitis in 28 per cent. Many of these allergic children will follow these two diseases by other allergic manifestations. His series shows 42 per cent of the children with recurrent upper respiratory infections on an allergic basis subsequently developed asthma or some other major allergic disease. It is generally accepted that the tendency to suffer from allergic disease is inherited. Every human being is, in all probability, potentially allergic, for under certain conditions of health and environment, allergy sensitivity may be acquired. He emphasizes that once the allergic state is established it tends to be followed by the development of

other allergic diseases. About 15 per cent of his experimental group developed major allergic diseases before the age of ten years as compared with about 60 per cent of the control group. The environment of the potentially allergic child deserves careful observation. Attention to these important factors may often forestall the appearance of allergic complaints. Glaser has reported that allergy to drugs occurs at least eight times more frequently in allergic children than in nonallergic children. Other than aspirin, penicillin is the drug used most commonly in the practice of pediatrics. Aspirin, however, does not possess a high sensitization potential in children according to this author.

Glaser believes that the intestinal tract during infancy, as well as in later life, is permeable to the passage of unaltered protein. By feeding the newborn infant a substitute formula for cows' milk, the development of allergy was delayed or largely prevented in early infancy. Infants so fed develop approximately only one-quarter as many allergic diseases in later infancy and childhood as infants started from birth on cows' milk formula. Glaser and Johnstone[57] subsequently stated that they did not choose at random which infants were to be in the experimental group, the sibling control group and the nonrelated control group in this attempt at prevention of allergic disease. Here they answer in rebuttal the suggestions and criticisms that had been made subsequent to the above-mentioned article.

Burrage, Burgin, Wang and Irwin[23] discuss the allergic diseases of infants and children. In eczema, the most important tool available for etiologic diagnosis is the history. This should be all-inclusive. They emphasize the importance of inhalants in atopic eczema and differentiate the lesions of eczema in early infancy from those appearing in childhood. If properly employed, skin tests may be of definite aid in the diagnosis of infantile or childhood eczema. It is important to realize, however, that a positive test does not necessarily confirm its etiologic significance; but the presence of a positive skin test often does help to establish the diagnosis of "allergy." The treatment of eczema is unsatisfactory from almost all standpoints. The authors warn against vaccination for smallpox in the eczematous child. They also point out the possible difficulty that may arise from the use of antiviral vaccines using chick embryos as a growth medium. This is particularly true in the egg-sensitive patient. Early diagnosis and treatment of bronchial asthma in infancy and childhood is imperative. These authors adequately discuss and cover the diagnosis and treatment of the main allergic diseases. When a specific antigen and antibody unite, it is thought that one or more chemical substances are released. These latter may be responsible for a series of changes including edema, smooth muscle spasm and hypersecretion of mucus. Though hyposensitization is often effective in many cases of allergy, the exact mechanism of hyposensitization remains an unexplained phenomenon. Vascular changes, smooth muscle spasms and excessive mucus in asthma are some of the pathologic changes that may occur even though the causative factors for the symptomatology are unknown.

CLIMATE IN ALLERGY

A problem with many controversial aspects is the influence of climate upon childhood allergy. Marks[107] reports that few children with allergic diseases will show improvement because of migration to the south Florida climate. If climate does favor improvement, it is largely because of re-

duced incidence of upper respiratory infections. Most of the migrant allergic patients either are not improved or are made worse. There seems to be a direct correlation between humidity and house dust sensitivity. In the basic sense, childhood allergy does not differ from adult allergy, though the habits, occupation and physical factors incident to age have to be considered in evaluating influences. If all other means have been exhausted in the patient's former place of residence, Marks recommends the southeastern section of Florida as a beneficial site for convalescence or residence. Florida is no place, however, for the "trial and error" method of therapy. In southeastern Florida, house dust is the all-important inhalant allergen. He does not believe that molds, in this section of the country, are of unusual significance as an etiologic factor of childhood allergy. They do rank secondary to house dust as an offending allergen. The individualization of these patients is all important. Though climate is a weapon of considerable virtue, the potentialities of this agent in allergy remain to be further explored.

Climate chasing has been pursued by physicians and the public as a cure for bronchial asthma. This often results in disappointing findings. An editorial[37] reports that very few patients are improved, and some are even made worse, by a change in climate. A careful etiologic inquiry will reveal that the real cause of cure when changing climate is the avoidance of certain allergenic factors in the patient's home and environment. Any patient who contemplates moving for reasons of health, first should determine whether the new climate will effect improvement and whether he can live in this community without becoming a ward of a local charity. It is essential that the physician should recognize which patients will benefit from a change of climate before such a move is recommended.

Johnston and Watkins[80] studied a large group of children to determine the effect of tonsillectomy and adenoidectomy upon the original complaint. Parents reported that there was a marked reduction in the incidence of respiratory infections. In contradiction to the parents' impression, however, the group of children, upon being rechecked, failed to show any diminution in the frequency of respiratory infections. There was a noticeable reduction in the amount of bronchitis in 85 per cent of the children. The results of operative procedures for the removal of tonsils and adenoids on asthmatic children are reported by these authors. In thirty-one children, twenty-six were somewhat improved.

Any ear condition not responding to customary otologic therapy should be further investigated from the allergic standpoint. This is the opinion of Elkins.[44] A diagnosis of otologic allergy may be difficult since acute phases are subject to spontaneous remissions. A complete history is of marked importance followed by visual and cytological examination. Allergy is often indicated by massive or moderate numbers of eosinophils, but this does not supply the type of allergen. At the same time, the absence of eosinophilia in the nasal smear does not rule out the allergic condition, but may lead to further consideration of other types of vasomotor conditions.

Dent[34] believes that visceral larva migrans should always be considered in those children with a high degree of eosinophilia. These children become infected by swallowing dirt contaminated with feces of a worm-bearing dog. Most of the patients reported by him were in the age group eighteen months to six years, during which time these children are most likely to swallow dirt. In so doing, the patient swallows embryonated eggs

which are usually found in moist dirt contaminated with dog feces. The larvae then hatch and penetrate the mucosa of the intestine. The adult worm never exists in the human intestine, since man is an unnatural host. It is therefore fruitless to examine the stools of humans for adult worms and ova. The ultimate prognosis in these patients is good. If the source of contamination is removed, these children may be expected to recover though it is conceivable that irreversible changes may be produced.

PSYCHOSOMATIC ASPECTS

For adequate relief and proper allergic therapy, the allergist must be expert not only in the field of allergy but also be an expert psychotherapist. Kaufman[82] feels that a skillful combination of allergy and psychotherapy will provide the greatest possible benefit to allergic patients. Unfortunately, many allergists are afraid to do psychotherapy. He states that the human psyche is quite resilient and hard to damage in a permanent manner. The type of psychotherapy used in allergic patients need not be more subtle or extensive than that required for the solution of the patient's current problems. One of the most neglected aspects of the treatment of allergic disorders is the management of the emotional reactions of the patient's family to his illness. Excessive sympathy and overprotection are factors that may be injurious to the patient. Their anxiety regarding his illness may be transferred to the patient and thus aggravate his complaints.

Religious people tend to fall in the classification of "perfectionists." O'Leary[110] states that perfectionists are usually idealists and do not like to be average. Another characteristic of this group is the tendency to be hypercritical of themselves or to overstress their failings. This idea is expressed symbolically in a formula such as "x - y = z." Here Father O'Leary uses "x" to represent the dream self, the hoped-for self or the desired self. "Y" represents the self as the person sees it, and "z" represents the reaction to the difference. The most important thing in this formula is not the absolute value of either x or y but the relative values of each. This makes the minus sign of the formula significant. "Y" is also important in that it represents not the person as he is but the person as he sees himself with relation to the person he hopes to be. With religious people, religion cannot be used to help them as a part of their treatment. The emotional side of the patient is very important in allergic diseases and must be taken into consideration. Treatment of allergy is like treatment of any other disease in that we must treat the whole person and not merely the disease. Too much attention to himself may cause a patient to have emotional upsets. By forgetting himself he will become more efficient and peaceful. Religion can be used in this type of patient as a therapeutic measure. The patient can be led to divert attention from himself to the work he has to do for the world and for God. Religious feelings may intensify one's dissatisfaction with himself and thereby intensify the allergic complaints that he may have. Properly handled religious ideas, on the other hand, can be used for therapeutic purposes to great advantage.

Speer[144] presents the clinical histories of six children to illustrate the syndrome of allergic tension and fatigue. Allergic tension represents a widespread exaggeration in motor activity and a corresponding increase in sensory reactivity. Allergic fatigue, on the other hand, is marked by a sensation of being tired and torpid. The state of tension seems to be made up of a motor component and a sensory component. With increased

motor activity there is an inability to relax. When this reaction is dominant, the physician can see for himself the problem that confronts both the parents and the teacher of the allergic child. Speer does not attempt to explore the techniques of diagnosis and treatment. Before an allergic origin is considered in a behavior problem, however, differential diagnosis must exhaust a wide variety of psychic and somatic influences. The demonstration of the role of specific allergen in a clinical manifestation of tension and fatigue is confirmation of such a diagnosis. Milk, chocolate, egg and corn were the foods most commonly offending in this condition.

Abramson[1] believes that much of the confusion and disagreement in the field of psychosomatic medicine could be reduced if verbatim transcripts as a scientific frame of reference were made available to the allergist. The concept of maternal rejection is difficult to use in brief psychotherapy with the parents of allergic children. The notion of engulfment and domination can be readily utilized by the allergist, making it thus more acceptable to the parents of allergic children. If the proper use of this engulfment theory by the parent and the physician fails, another mode of therapy should be tried. The true goal of therapy is a lessening of the threatening nature of rage, engendered by frustrations undergone by the parents and the derived rejection of the child. Parental rejection may occur when the parent becomes enraged at the failure to form the character of the allergic child into a pattern based upon the parent's own narcisistic needs.

TESTING EXTRACTS

From the result of their investigations Tuft and Heck[157] conclude that patients can and do acquire sensitization to new food allergens. The data from a circulated questionnaire revealed that most allergists believe skin test reactions lessen in degree. Do these reactions differ as the result of food avoidance? The minority opinion is that the skin test reaction lessens because of food avoidance. In contrast, the majority of allergists felt that specific treatment brought about or was followed by a reduction in the skin test reaction. Unsatisfactory treatment results or the appearance of new symptoms were the two main reasons why most allergists retest their patients. About one-fourth of the allergists answering this questionnaire expressed the viewpoint that food tests either were without value or were of such doubtful value as to be entirely unreliable. They are, in some instances, misleading. In this reviewer's experience within the past ten years, less and less testing seems to have been done. Adequate testing can be accomplished with the major important factors found in the patient's diet and environment, with useless testing being eliminated for those materials that are seldom and infrequently used. I am in agreement with the need for streamlining our testing methods and materials in order to shorten the investigative procedures. At the same time, the allergist should know which skin tests are considered worth while. Proper standardization of testing materials is a necessity in order that all men in the field of allergy may use uniform materials for tests and obtain, it is hoped, uniform results. One should not rely upon a reduction in skin test reaction as a criterion of improved tolerance to permit re-addition of a food or as a guide in pollen therapy. In patients over fifty, the skin test reaction will show a marked lessening in degree.

The standardization of a dust extract poses a more difficult problem

than that of the pollens. Wodehouse[167] states that pollen extracts may vary widely in total activity. Their antigenic structure, however, is not likely to deviate widely from a mean unless the material is grossly mishandled in collection or preparation. House dust extracts are apt to vary more widely, not only in total activity but also in antigenic patterns. The source of the raw material is the factor upon which the antigenic pattern is dependent. Old house prepared dust extracts obtained from many sources were used in this particular study. These he compared diffused against various rabbit antisera. He has stated that standardization of dust extracts may be accomplished by setting aside, in liophilized state, pooled antidust rabbit serum made with a selected dust extract. Identification and assay of any unknown dust extract in terms of the designated standard may then be made upon its precipitation pattern and the graph of its penetration rate in relation to its concentration.

Axelrad[6] describes a new allergy syringe for testing and treatment. Using Corsol packing, this author has found that his syringe has no effect on various extracts nor on parenteral solutions used in general practice. Corsol is a new inorganic rubber which, when attached to a metal plunger, tightens the seal in the syringe by a very slight right turn. A very slight turn to the left loosens this same seal. The low cost and an easy interchange of parts seem to be advantages in this type of syringe.

ELECTROLYTES AND PHARMACOLOGY

A review of our present knowledge in the physiology and patho-physiology of fluid and electrolyte metabolism is presented by Wittich.[166] This is an important feature of the over-all therapy of allergic diseases. Dehydration due to lack of fluid intake will disturb the electrolyte balance in allergic patients. Abnormalities will also be noted where there is a loss of fluid in profusely "weeping" eczemas or where there is a water loss due to diarrhea. Angioedema is a result of escape of fluid into the paravascular or extracellular compartment. This represents a loss of potassium. A life-saving measure in acute and generalized infantile eczema, particularly if associated with diarrhea, may be the administration of Butler's, Darrow's or Baxter's electrolyte solution No. 2. Patients on cortisone respond better when given extra potassium in relatively low amounts along with a minimum sodium intake. In the asthmatic patient, dehydration results from a lack of fluid intake by mouth, sweating and other means of fluid loss. Intravenous introduction of 5 per cent glucose in normal saline or distilled water will produce adequate hydration. The sodium-potassium ratio may be disturbed in a serious manner if there is a definite potassium deficiency. If an allergic patient is placed upon an elimination diet which is poorly balanced and inadequate, then decreased potassium intake and accelerated excretion will be the two causes of potassium loss from the intracellular and extracellular compartments. Potassium is important because of its function to aid in the maintenance of normal water balance and distribution. Normal osmotic equilibrium and normal acid base equilibrium are also dependent upon the potassium deficiency. Replacement potassium therapy should not exceed 100 milliequivalents of potassium intravenously in twenty-four hours and no more than 40 milli-equivalents per liter of intravenous fluids. The rate of flow is important. This should be under twenty drops per minute to avoid danger of hyperpotassemia because of the slow rate of absorption of potassium. A knowledge of fluid and electrolyte metabolism is thought by Wittich to be a definite adjunct in the treatment of the allergic patient.

The pharmacology of the involved process and the reason for the development of the sensitized state are the two divisions discussed by Trethewie.[156] Upon exposure to antigen, the organism develops an abnormal immune response; and when the antigen meets the antibody on the cell surface, profound changes occur and preformed H substances are released. These latter are stated to be histamine, SRS, heparin and probably many other substances. This author believes that there may be a biochemical difference in allergic patients as an explanation of the development of the allergic state.

Research on allergic diseases and all problems connected with this subject should deal with two aspects: first, a clinical aspect involving diagnosis, development of the disease and treatment; secondly, the theoretical side concerning etiology, physiology and pathology. Mayer[109] believes that the clinical aspects of allergy are quite well understood. There are certain pathologic processes which are not classified as allergic diseases although they present many symptoms or aspects suggestive of allergic origin. Here the question arises whether such diseases may not belong to the hitherto unrecognized group of allergic illnesses. Lupus erythematosus, agranulocytosis, multiple sclerosis, sarcoidosis and many others may be questions of true allergy or specific hypersensitivity constituting a problem for future research in allergy. In all of these, the disease develops only after a long incubation period which may last many months and then only in a small proportion of the total number of individuals so studied. This is Mayer's first criterion. His second is that reactivity is specifically directed against the causative agent, and there is a specific cross-reactivity. Since evidence has not been established for these diseases upon an allergic basis, we must continue to consider them as the result of primary toxic reactions which mimic an allergy in their occurrence. Such reactions do certainly exist. Fixed drug eruption is another important, still unexplored field. Few substances produce allergies in such a most characteristic aspect. He feels it to be unfortunate that little theoretical work in allergy emanates from allergists themselves and from allergy units. This feature may change if the basic concepts of the American Foundation for Allergic Diseases are fulfilled.

Acute allergic emergencies are fortunately relatively rare despite the high incidence of allergic disease. Talmadge[153] discusses the treatment of allergic emergencies as related to asthma, urticaria, angioedema, anaphylactoid reactions to drugs and contact dermatitis. Symptomatic treatment of asthma is stated to be dependent upon the following features: (1) providing adequate oxygenization of the blood, (2) reassurance, rest and sedation, (3) correct dehydration and maintainance of adequate fluid and caloric intake, (4) relief of bronchospasm. Talmadge states, "Almost without exception, patients in status asthmaticus are not significantly relieved by epinephrine and related drugs." The patient in an acute attack of asthma or even in status should be given an adequate trial on epinephrine, because it is felt that this drug is the best friend that the allergist has. All too often, the "epinephrine-fast" patient has not been given an adequate trial. No mention is made of the use of ACTH either by intramuscular or intravenous route in the care of the asthmatic patient. There are many patients who will fail to respond adequately to the oral or intramuscular administration of cortisone but will respond in very fine manner to the use of this pituitary hormone. I agree with Talmadge when he states that the antihistamines are without value in relieving the acute attack of urticaria, particularly that due to penicillin sensitivity. Cortisone or ACTH is

the treatment of choice in this particular condition. Penicillin sensitivity must be considered in any acute urticaria, at the present time, because this drug is the most frequent cause of severe urticaria. This is especially true if the onset of the skin lesions is noted seven to twenty-one days after the use of the drug in any form. The absence of an antigen-antibody demonstrable reaction makes it uncertain whether a procaine sensitivity is a true allergic reaction or a cellular idiosyncrasy to this drug. This author advises the administration of Amytal® or Nembutal® before the use of procaine and related drugs.

In cases of nasal obstruction, simple examination of the nostrils may reveal the cause of the obstruction to be deviation of the nasal septum or nasal polyps. Strong[148] writes that the treatment of the nasal septum must necessarily be correction of the mechanical difficulty by surgery. Vasomotor rhinitis may be allergic, endocrine or emotionally based. In these instances, the membrane presents a bluish dull appearance. The effect of desensitization on nasal obstruction usually is not as rewarding and dramatic as in several other allergic manifestations. This reviewer feels that the most obstinate feature of seasonal hay fever is the marked nasal obstruction that may be associated with pollen sensitivity. Other symptoms of seasonal hay fever seem to be readily relieved by specific therapy, but few patients will have complete relief of the troublesome nasal obstruction. Similarly the benefit afforded by antihistamines is usually disappointing in relieving this complaint. Vasomotor rhinitis may be of sufficiently long standing that irreversible changes occur in the mucosa. The chronically edematous and congested mucosa becomes organized in its hypertrophied state. Permanent shrinking of the mucosa may be done without producing any damage to the surface epithelium. Submucosal electrocoagulation, using a diathermy current, is the most satisfactory method of carrying out this procedure. The result is usually quite satisfactory. This author states that antibiotics have changed the pattern of otolaryngologic therapy and have broadened the horizon of the specialty. This reviewer might add that the recognition of respiratory allergy has also changed the pattern of otolaryngologic therapy as well as practice.

TOBACCO EFFECTS

Two hundred consecutive private patients were tested by Rosen[125] in order to discover the value of the intradermal test with tobacco smoke or leaf extract. Good positive reactions were obtained upon thirty-eight patients, of whom four had clinical symptoms which cleared completely on discontinuing tobacco. Their complaints could be readily reproduced by resuming the use of tobacco. Desensitization procedures were without value. Sensitivity to smoking may be suggested by an exaggerated increase in the pulse rate, a greater drop in skin temperature or electrocardiographic patterns before and after smoking.

According to Greene and Berkowitz,[62] tobacco bronchitis is associated almost entirely with deliberately inhaled smoke. They advise against the use of tobacco by asthmatic patients and by those with infectious bronchitis, emphysema and occupational dust inhalation. Though it has been stated that tobacco smoking seldom if ever affects the lungs, it is their impression that pulmonary emphysema is unusually frequent in inveterate cigarette smokers with marked bronchitis. Tobacco bronchitis disappears with abstinence from tobacco. This is true regardless of the length of time that the patient has used the weed. They studied 4,322 pre-operative patients with the aid of a test cough of proved sensitivity and reliability.

They believe that smokers' bronchitis is the result of inhaled smoking, since it is rare in cigar and pipe smokers. In this latter form of tobacco usage, inhalation of the smoke is seldom accomplished. It has long been recognized that certain people cannot use tobacco without getting respiratory, cardiovascular or other symptoms from its use.

Rosen[126] believes that these patients' symptoms caused by tobacco usage are the result of definite allergy to tobacco smoke. Positive skin tests to tobacco leaf extract were found in 19 per cent of 200 patients. It is recognized that tobacco extract positive skin tests do not correlate with clinical symptoms nearly as well as atmospheric pollen mold or environmental dust or feather reactions. An exaggerated increase in pulse rate or a great drop in skin temperature of the extremities after smoking are two features which are helpful in determining the patient who should cease smoking. Rosen was able to reproduce, by smoking, the symptoms of asthma, cough, migraine and urticaria in his patients.

Respiratory function tests were made before and after smoking three cigarettes by ninety-one patients and reported by Bickerman and Barach.[13] Ten of these patients showed a reduction in vital capacity and maximum breathing capacity following the use of tobacco. These findings were not accompanied, however, by a perceptible increase in the severity of their original asthmatic symptoms. The production of mucoid or mucopurulent sputum by tobacco smoking was thought to be the cause of increased vital capacity in nine patients.

Much has been written in the recent literature concerning the use of ACTH and cortisone as agents containing antipyretic properties. Waugh[163] has reported an instance wherein the oral administration of cortisone had no apparent effect upon his patient's heat pyrexia. Any beneficial effect of corticotropin or of cortisone when used as an adjunct might be due to the prevention of pituitary-adrenal collapse.

Allergy and diabetes are two of the most common disease states in which a definite hereditary constitutional factor appears to be operative according to Siegal and Herzstein.[138] For this reason they studied the incidence of allergic symptoms among diabetic patients. They found that eight of forty diabetic patients had either clinically manifest or latent atopy. An almost identical incidence of allergic disease, namely 20 per cent, was found in parallel observations in a nondiabetic control group. They concluded from these studies that there existed no special relationship between the two hereditary states of atopy and diabetes melitus. For this reason, it appeared unlikely that diabetes of the severe type is based on an immunologic mechanism.

Impending abortion was prevented and controlled by the administration of antihistaminic drugs in two patients as reported by Herrod.[71] One of these patients had hay fever. Hyposensitization therapy resulted in a constitutional reaction during which the patient developed severe uterine cramps. Intravenous antihistamine therapy relieved all symptoms including the uterine cramps. He suggests that allergy, or at least histamine, was the precipitating factor in these cases of threatened abortion.

It will be noted above that Mayer suggested that sarcoidosis might be upon an allergic basis. Kass, Jackson and Slavin[81] present three cases with evidence suggesting the sarcoidosis and sarcoid lesions belong in the group of hypersensitivity diseases and reactions. In one of their cases, the earliest hypersensitivity symptoms noted were those of erythema nodosum and hilar adenopathy. The second case showed a marked antecedent sensitivity to dust, milk and milk products. They do not imply by this, however, that

sarcoidosis occurs only in people with allergic backgrounds. Their third case differed from the other two in that the lesions of sarcoidosis appeared to be localized. This local tissue response is termed a sarcoid lesion as opposed to sarcoidosis; it may indicate a hypersensitivity reaction resulting from the presence of irritant products in the tissues. In speaking of the use of cortisone in these patients, it becomes increasingly apparent that the connective tissue is not stable but exists in a labile state which is under the control of the opposing hormonal forces. These authors believe that the hypersensitivity agent causes, in susceptible persons, an antigen-antibody reaction with increase in gamma globulin, eosinophils, plasma cells and leukocytes. Also in line with Mayer's suggestion that other conditions might be upon an allergic basis, Wiseman and Moore[164] present a patient with recurrent simple congestive glaucoma, who appeared to be getting progressively worse until brought under allergic management. Glaucoma causes at least 12 per cent of the blindness in the United States. If their concept is correct, it would appear that certain blood vessels of the eye can act as an allergic shock organ thereby producing increased ocular tension. This phenomenon is more likely if allergy is concomitantly causing active symptoms in some other organ of the body. Their patient, a sixty-four-year-old white man, had had two bouts of asthma during the preceding six years, each attack lasting several years. He had had recurring attacks of glaucoma since about seven years prior to being first seen by these authors.

Another disease in which many allergists have felt there is a strong allergic background is that of epilepsy. Peterman[115] says that it makes no difference to the epileptic whether he has inherited the disease or a tendency to the disease. Treatment and supervision of the epileptic patient must be continued indefinitely. (The same may also be said concerning the allergic patient in most instances.) Even when seizures in the epileptic patient are completely controlled, the "tendency" is transmitted to their progeny as evidenced by this series of cases. They show that 50 per cent of the patients with genetic epilepsy give a history of familial epilepsy.

Kilbourne[85] feels that the use of antibiotics in the allergic patient is really a therapeutic dilemma. The hazard of drug hypersensitivity is increased at the same time as the need for antimicrobial therapy of secondary skin and respiratory tract infections. Virtually all reactions in his experience have been due to parenterally administered penicillin. The higher incidence of penicillin-induced reactions may be related to the more prolonged and extensive exposure of the population to this drug. Kilbourne also believes that the parenteral route of administration may be a factor in this high incidence. He advises the critical employment of antibiotics in the allergic patient and the use of them only when clear indications are present. Combined or multiple antibiotic therapy should be avoided. He prefers the oral route of administration if such measures are feasible. Promiscuous use of topical antibiotic preparations is deplored, and he advises marked precautions when parenteral antibiotic therapy is given to asthmatic patients.

ALLERGY AND INSURANCE

Migraine is not specifically a vascular disorder but has a prominent vascular component in the opinion of Ungerleider.[160] The individuals with a history of migraine show a normal life expectancy and in some categories even a better than average mortality ratio. This author states that a history of asthma, unless attacks are numerous or severe, has no untoward

effect upon the mortality of the patient with bronchiectasis. This reviewer has always been confused as to why life insurance companies will persist in rating an asthmatic patient when, in reality, many forms of bronchial asthma have no effect upon the mortality of the patient. A previous review[66] and a classification of asthma by Brown and Halpin[20] would permit an insurance company to utilize a standard in the acceptance or rejection of asthmatic applicants for life insurance.

FOUNDATION

Progress in the field of allergy should interest every allergist in the world. Each of us is accomplishing a small bit in giving lectures to our patients or to lay groups and possibly in writing books on allergy. Postgraduate teaching in arranged courses, in schools and in clinics is mute evidence of the need for more allergy specialists. Greater facilities are needed for training in allergy specialization, but the individual allergist is unable to convince medical institutions of the importance of such facilities. The attainment of all of these factors, which constitute progress in allergy, is gained through the co-operative planning of the American Foundation for Allergic Diseases. This is the subject of an editorial[38] which states that the aims and purposes of the Foundation are the correction of those very deficiencies to which the above reference is made. It is necessary first that the idea of the Foundation be sold to the practicing allergist before it can be presented to the public. This Foundation is now in its second year of definite activity. The first year was devoted to public education in allergy by press, radio and the establishment of a scientific and educational council to deal with research and medical education.

IMMUNIZATION

Blankenhorn and Knowles[15] discuss forty-five cases of periarteritis nodosa, which they have divided pathologically into two groups. These groups comprise patients with classic periarteritis nodosa and with hypersensitivity angiitis. In this latter classification, if hypersensitivity angiitis is recognized at a sufficiently early time the improvement may be remarkable. Hypersensitivity angiitis is a sensitivity reaction. They were unable to obtain any biopsies from patients with this diagnosis because the disease was usually fulminant and not recognized. The main characteristics of hypersensitivity angiitis were fever, skin rash, nephritis and myocarditis. Frequently the history suggests recent exposure to some antigenic substance.

An editorial[39] describes collagen as a term applied to all the extracellular components of connective tissue. The collagen diseases, therefore, are systemic diseases of the connective tissue. In these conditions, of which there are many, widely different clinical manifestations have certain features in common and possibly a common pathogenesis. Hence many observers have thought that this common pathogenesis was related to the phenomenon of allergy. This assumption, however, has not yet received universal support nor does it explain the various locations of the arterial changes in different collagenic syndromes. This common pathogenesis, if it be a phenomenon of allergy, does not explain why periarteritis nodosa is so often progressive while serum sickness is self-limited and relatively benign.

Multiple antigen preparations for diphtheria, tetanus, pertussis and others cause little more reaction than antigens used singly. Antibody production is equal to or better because of the adjuvant effect. Top[155] dis-

cusses the age at which immunization should be instituted. The age at which innoculation of antigens should take place is one of a number of facets in the general consideration of active protection against communicable diseases. He recommends the early use of pertussis innoculations, preferably within the first six months of life. His reasons for this early innoculation are that newborn and young infants have little or no inherited immunity to pertussis and most complications and deaths occur in the very early age group. It is necessary also to innoculate for diphtheria at an early age since infants of susceptible mothers are not immune. However, it has long been recognized that the presence of maternally derived antibodies interferes with neonatal innoculation against diphtheria. The primary dose of diphtheria toxoid should be given at about the age of six months, although an earlier administration of this preparation might be desirable. Two doses of alum-precipitated toxoid should be administered at monthly intervals and booster dosage should be given twelve months after the primary injection. Age is not a factor in antigenic response for tetanus toxoid so the primary innoculations may be given at any time. Alum-precipitated toxoid is given in two doses, spaced one month apart at any time during the first year of life with resulting high titers. Booster dosage should be given at three-year intervals and after any injury. In those who have received the basic immunization and maintained it by quadrennial boosters, satisfactory protection should be afforded by tetanus toxoid given at the time of injury. This is the opinion of Love, Shaul, Margileth and Martelle.[95] They also state that recall injections are effective in eliciting satisfactory titration levels if given as long as ten years after a basic series. They warn, however, that booster injections after a four-year lapse may not bring out a satisfactory protective level within the incubation period of some cases of tetanus. Love and his co-workers recommend that pertussis antigen should be omitted from the combined preparations after the child has reached the age of five. Combined diphtheria-tetanus toxoid can be given when the child is nine or ten. Thereafter boosters of tetanus toxoid and of diphtheria toxoid, if indicated, should be repeated quadrennially until the age of thirty-five. They describe in detail the immunization procedures which are mandatory in various countries throughout the world, and present suggested tables for immunization for international travel. They stress the importance of immunization procedures, giving the dosages and techniques of administration.

Dougherty[35] describes the new tuberculin test in which all of the elements present in the tuberculosis bacillus and its capsule are injected intradermally. It is read in forty-eight hours and again in three weeks. The forty-eight hour reaction denotes the allergic response to tuberculosis infection while the three-week reaction is indicative of immunity to the disease.

An editorial[40] calls to mind that there are no safe wounds of traumatic origin if there has been a break in the skin. Fifty-one cases were reported by the University Hospitals at Iowa City during the past eleven years. Various, and often minor, insignificant wounds were the points of entrance for the tetanus infection. In eight of the fifty-one patients, antitoxin had been administered between the time of injury and the onset of infection. It is their contention that the standard dosage of 1500 units of antitoxin should no longer be considered an adequate routine dose. At least 3,000 units should be regarded as minimum. Manipulation of a previously infected wound should call for a repetition of antitoxin immunization or, in the actively immunized patient, a booster injection of toxoid. Hypersensitivity to serum further reduces the effectiveness of passive protection.

They consider it unwise to count on more than five years' duration of active immunity following toxoid immunization. They recommend that small children should have a routine booster injection annually, preferably in the spring. Adults should have a renewal or booster toxoid injection at least every three years and annually if they are engaged in hazardous occupations. Another editorial,[41] calls to mind the fact that tetanus toxoid cannot be used to prevent tetanus if the patient has never before received the material. The author states that active immunity when induced by tetanus toxoid is a relatively slow process which requires weeks or months. It has been thought in the past that there is a stimulus from a possible tetanus bacillus infection, but this is now considered to be inadequate. There is no substitute, with the possible exception of tetanus antitoxin, for a booster dose of tetanus toxoid when definitely indicated. Since tetanus is not an immunizing disease, tetanus toxoid must be administered despite recovery from one or more attacks of tetanus. When a patient has not received at least one injection of tetanus toxoid, antitoxin and toxoid should not be administered at the same time. The antitoxin will interfere with the toxoid, but the toxoid will not interfere with the antitoxin. It is recommended that every patient who receives tetanus antitoxin should return to the physician's office to receive tetanus toxoid at a later appropriate time. This one measure will prevent the hazard of acute serum sickness.

Two additional cases are reported in which nervous system complications follow the therapeutic or prophylactic administration of foreign serum. Plitman and Gendel[117] state that serum disease of the nervous system occurs predominantly in individuals over twenty-one years of age. Though both the central and peripheral nervous systems can be involved, the most common type of complication is that of the roots comprising the brachial plexus. Pain across one or both shoulder girdles is usually followed within hours or days by the appearance of paralysis. The prognosis in serum disease of the nervous system is usually good with complete recovery of function occurring even in view of central nervous system involvement. Park and Richardson[113] also review the neurological complications of serum sickness. They state that serum neuritis is the most common type of involvement of the peripheral nervous system. They report two cases with focal cerebral injury following serum sickness. They believe that the allergic reaction is located in the shock organ which, in these cases, was believed to be the blood vessels of the wall of the major cerebral arteries. Undesirable local and constitutional reactions have been observed with the use of influenza virus vaccine.

Mansmann[104] initiated studies of influenza virus vaccine immunization on allergic patients. He noted three types of sensitivity reactions: (1) reactions to fowl sensitivity, (2) reactions to the preservative or inactivator chemicals in the vaccine menstruum, and (3) the delayed reactions. From his studies he believes that if the persons clinically sensitive to fowl are eliminated, it is safe to begin immunization with the 1-100 dilution of the A and B influenza virus vaccine in any patient. This is correct whether he be allergic or nonallergic and whether the patient be adult or child. The dosage is then raised gradually through the serial dilutions until 1 cc total concentrated vaccine has been given.

RESPIRATORY ALLERGY

Rapaport[121] writes that there has been a growing awareness during the past decade that causes other than allergy may initiate or express themselves in asthma. However, atopy and infection are usually the most sig-

nificant primary factors. He believes that it is important to recognize that asthma is essentially a part of a syndrome. It is particularly true in children that some of the earlier physical findings may be readily observed. These are not definitely identified at first as part of the asthma syndrome. He quotes Peshkin as having divided the asthma syndrome into three stages; namely, the oppression stage, the wheezing stage and the attack stage. Rapaport believes that the problem of asthma resolves itself in the physician having a knowledge of the multiplicity of possible causes and an awareness of these in the evaluation of each individual problem.

CLASSIFICATION OF ASTHMA

It is the contention of Swineford[152] that asthma is not a disease but is a syndrome in which wheezing is the diagnostic feature. He believes that any syndrome which is characterized by wheezing should be called asthma, particularly if the wheezing is accompanied by dyspnea. In discussing the classification of causes, he reports upon the different types of causes of wheezing as well as discussing the rather confusing literature on the classification of asthma. He also has suggestions for resolving and avoiding existing and future confusion. He emphasizes the facts that the causes of wheezing are numerous and that the recognition of these causes is simplified by classifying them. History and physical examination will, in themselves, give a reasonably accurate classification. Most patients with asthma have multiple causes for the production of their complaints. Detailed studies of more than 5,000 asthmatic patients form the approach to this study by this author. Since most asthma is due to atopy or infection, this is Swineford's first classification. The dominant causes of asthma may be reflex, physical, psychogenic and chronic lung disease. He contends that the role of the psyche in asthma lies somewhere between the views of the faddists, who feel that most asthma is psychogenic, and the reactionaries, who believe that the psyche plays no role in the production of complaints. Cardiac asthma, bronchial obstruction and idiopathic sources cause forms of wheezing. He is of the belief that the terms extrinsic and intrinsic, as regards classification of asthma, should be abolished. In the classification described by Swineford, the criteria by which the impact of each of the several types of causes of wheezing may be recognized are discussed in detail. By "cause" is meant the true etiologic factor such as house dust, ragweed, eggs, nasal polyps and other such substances. By "type of cause" of wheezing is meant atopic reflex, physical, psychogenic or infectious. By the use of such a classification a logical approach to a long detailed search and analysis for the causative and contributing factors can be followed to the end.

The types of wheezing will fall into at least eight clearly defined syndromes according to Brown and Halpin.[20] Though they overlap, their individual features are so distinctive that they can be differentially diagnosed. The types of wheezing in this report are said to be atopic, infectious (acute and chronic), psychogenic, physical, nasogenic (or reflex), cardiac, locally obstructive, and asthma due to drug reactions. Each of these is defined in turn with the understanding that they represent only skeleton outlines and that qualifying terms must be used. Each of these types of wheezing is thoroughly presented under the headings as follows: personal history, family history, onset of wheezing, clinical course, physical examination, pathologic findings, laboratory data, skin tests and response to treatment. Since all of these syndromes can conceivably overlap, an atopic patient can become infected, inspire a foreign body, be emotionally upset or de-

velop cardiac lesions. Using this classification, the authors state that the subject should be headed: asthma, atopic with acute infection; asthma, atopic with psychogenic factors; asthma, infectious with psychogenic features; or asthma, infectious with cardiac disorders. The traditional numbers 1, 2 and 3 are used for mild, moderate and severe asthma with status asthmaticus keeping its present label. The term mild or grade 1 would refer, therefore, to a mild response upon major exposure in quantity or time. It would also indicate quick recovery following elimination of exposure. Freedom from symptoms until the next exposure would be observed. Grade 2 or moderate asthma would respond more vigorously to less exposure—such patients when sensitive to pollen would begin early in the season, respond less completely to air-conditioning, require larger dosages of medication and small doses of ACTH and cortisone. Their symptoms would extend beyond the season because their lungs are "triggered" and because other causes exist. Grade 3 or the severe asthmatic patient would respond more vigorously to allergens and stay ill longer. Brown and Halpin criticize any form of a workable classification. They state that the first criticism of such a system may be the awkwardness of its use. However, the awkwardness may be due to inertia rather than to a fault inherent in the codification system. Such classifications may not include every present or conceivable possible future asthmatic state. The third criticism is the question of "why use any classification at all?" The classification as described by these authors would be used universally if each asthmatic attack was defined as to the chief etiologic factor, the contributing or causative factor, the degree of patient response, the predominant tissue effects and the progressive pathologic changes which occur.

In infancy, the diagnosis of asthma is based upon the recurrence of wheezing and the demonstration of the patient's allergy. In addition to these two foundations, the patient should not have any other condition which would cause wheezing. Buffum[22] states that the difficulty may be in demonstrating the allergic state even though the wheezing is not characteristic. The necessity of making a tentative diagnosis is obvious, and the definite diagnosis may require a period of several weeks or months. Asthma of purely infectious origin becomes less common as the child gets older. Within a year usually either the wheezing has ceased to recur or atopic causes have made themselves evident. The diagnosis of asthma and also the etiologic diagnosis can be made.

CARDIAC VERSUS BRONCHIAL ASTHMA

The primary cause of cardiac asthma lies in the heart and in bronchial asthma in the bronchial tree. Ferris[47] states that rales are usually present in the cardiac type of asthma, while the primary finding in true bronchial asthma is the absence of any sign of congestion. Both types are characterized by nocturnal attacks, and each type is associated with definite wheezing. The air-hunger and dyspnea of the cardiac patient is due to pulmonary congestion. Therefore acute emphysema, so common in bronchial asthma, is seldom seen in the cardiac patient. In advanced stages of emphysema, pulmonary hypertension, decreased heart output and right ventricular strain may be the picture of primary heart failure as a result of pulmonary edema. Aminophyllin is the drug of choice in doubtful patients because it is an excellent bronchodilating drug and can be used safely in both cardiac and bronchial asthma.

McAuliffe[98] states that no physical examination of the chest is complete without the use of the expiratory cough to elicit rales. The stimuli that

produce cough in the average patient are inflammatory, mechanical and thermal. The mechanism of coughing, however, is controlled by a special nerve center located in the medulla oblongata. Cough should always be considered as a symptom. The two main types may be described as the one which rids the respiratory tract of offending materials and the ineffectual nonproductive cough. Only by a process of elimination, a careful history, physical examination, x-rays, and laboratory aids may the differential diagnosis of cough be accurately based. The causes of cough are so numerous that they cannot be listed specifically. Douglass[36] has pointed out that the reflex functions properly and spontaneously upon irritation of the afferent nerve fibers of the medulla. In some conditions cough serves a useful and necessary purpose. In others, however, cough is simply a useless byproduct of the accompanying and causative thoracic disease. Duration of cough is self-limited in those patients where this complaint is secondary to coryza and the variance of influenza as well as other inflammatory diseases. As in most conditions, the treatment of this complaint is to remove or cure its cause.

Longacre[94] points out that infection which precipitates an attack of asthma should not differ significantly from any other infection in the body. Antibacterial therapy in these instances must be specific against the infection. Failures in this form of therapy usually result from an inaccurate evaluation of the significance of the infection as well as a failure to administer an effective antibiotic against a particular infection. Failure is also observed when an effective antibiotic fails to reach the site of infection.

Shuey and Grater[137] have studied twenty-three patients who were treated for periods ranging from three to eighteen months. This treatment consisted of procaine penicillin in 300,000 to 600,000 unit doses three times weekly. Streptomycin, Gantrisin® and Bicillin® were also a part of their treatment study. The most feared complication of antibiotic therapy was anaphylaxis, but they experienced only one mild reaction to penicillin. Of the twenty-three patients studied under this regimen, sixteen obtained excellent results with four showing moderate improvement. One showed no improvement. In the great majority of their patients, no allergy could be demonstrated; and the number and severity of the asthmatic attacks were definitely lessened. In a study of 200 consecutive sensitivity tests made from patients with respiratory infections, Rosen and Carabelle[76] found that penicillin was specific in only 10 per cent of the cases. Streptomycin was specific in 33 per cent and a combination of these two drugs was specific in 30 per cent in those cases where both penicillin and streptomycin were negative. Chloromycetin was reported to be 80 per cent specific, with Aureomycin® 60 per cent, Terramycin® 70 per cent, Erythromycin® 34 per cent and sulfonamid 8 per cent. Allergy is very common in the upper respiratory infections of infants under two years of age. This is manifest by the presence of eosinophils. Without specific therapy, approximately 50 per cent of all upper respiratory infections become clinically cured within an average of eight days. They consider that infection is a marked aggravating factor in the field of allergy rather than a specific cause.

Lester[92] divides congenital deformities of the anterior chest wall into protusion deformities and depression deformities. Funnel chest is a characteristic of the depression deformities, whereas the protusion is usually in the mid-line or lateral to the sternum. Surgical procedures are necessary for good correction and relief of the physiologic disturbances. These congenital abnormalities are not related to acquired defects such as rickets or any other concomitant disease. There does seem to be a strong hereditary tendency in the types of deformity which occur in the family.

STATUS AND THERAPY

There are three objectives of treatment in status asthmaticus. The first is environmental control, the next is symptomatic relief of the patient's asthma, and the third is the control of complications and coexisting diseases which aggravate the severity of asthma. Carryer and his co-workers[24] state that proper control of the patient's environment will remove him from factors which may be aggravating the asthma and permit measures likely to relieve severe asthma. The desirability of hospitalization in severe asthma is emphasized. They state that epinephrine is the most effective bronchodilator in use today. They warn against the use of oxygen therapy in the patient with advanced pulmonary emphysema. Adverse effects often result from this therapy. Subsequent to surgery on the stomach, kidney, diaphragm colon or biliary passages, carbon dioxide is a valuable gas to be employed in these patients. Five per cent carbon dioxide in 95 per cent oxygen is a powerful respiratory stimulant, and a few inhalations of this gas at hourly intervals after operation will stimulate the respiratory center and thoroughly aerate the lungs. It is necessary to combat dehydration by adequate administration of fluids to the asthmatic patient. The treatment of the asthmatic patient should be directed not towards the asthma alone, since any proper program of treatment should consider the whole patient and should be modified accordingly. It is necessary for the allergist to interpret accurately the history, clinical findings and contributing factors of his patient's condition more completely than the man in general practice, if the allergist is to be of distinct assistance to the allergic patient. Lowance[97] believes that the allergist today has much to offer the allergic patient and the practice of medicine in general. He considers the distinguishing attributes of the skilled allergist to be his ability born of experience and concentration to prescribe the proper treatment for the particular condition. Soundness of judgment and confidence in his specialized knowledge are an inspiration to the patient.

In the acute attack of asthma in childhood it is necessary to correct the immediate environment as well as administer the proper medication. Levin[93] has described these measures very adequately. The drug of choice in the treatment of an acute attack of childhood asthma is aqueous epinephrine. The best dosage is the smallest amount that will give relief without undesirable side reactions. Levin advises against the use of morphine in the treatment of either childhood or adult asthma. He states that antihistaminics are seldom useful in asthma, particularly if the attack is accompanied by a respiratory infection. Should the child have a respiratory infection, it is useful to have available oral penicillin so that this therapy may be started at the very onset of the disease. He has never found it necessary to resort to bronchoscopy during status asthmaticus in children. With the various forms of medication, it seldom will be necessary to resort to this treatment of status asthmaticus in childhood.

Though ACTH and cortisone are potent effective weapons in the symptomatic treatment of bronchial asthma, Brown[18] does not consider them as substitutes for elimination of causative allergens or injection treatment. Their use as a substitute for these latter forms of therapy does the patient a major disservice. It is necessary that the physician have a knowledge of the physiologic inter-relationships, the endocrine effects and the pharmacologic results before ACTH and cortisone are used to any advantage.

The usefulness of Demerol® in the asthmatic patient is stressed by Herschfus, Salomon and Segal.[72] They demonstrate that this drug has both antihistaminic and anticholinergic properties. Improved vital capacity and

maximal breathing capacity with less wheezing were demonstrated after the drug had been employed. Respiratory depression does occur with Demerol if the dosage is too large or is repeated too frequently in patients with severe chronic bronchial asthma and associated emphysema. They warn against the use of this drug in combination with barbiturates or along with high concentrations of oxygen in patients with chronic hypoxia secondary to pulmonary emphysema. These authors state that Demerol in the proper dosage is a very useful and safe drug in the treatment in the acute asthmatic attack or status asthmaticus. This report on Demerol stimulated the International Correspondence Club of Allergists to circulate a questionnaire among the corresponding members. This reviewer agrees with the authors of the above article with emphasis upon the words "proper dosage" and "added caution." Demerol should seldom be used as the initial drug in an effort to relieve an acute attack of asthma; but if the patient does not respond satisfactorily or if a mild degree of sedation is warranted, then Demerol is a valuable adjunct to the therapeutic armamentarium.

Allergy to inhalation anesthetics is uncommon. Most drug reactions are encountered with local anesthetics. Adriani[2] states that there are no objections to the use of ethyl and vinyl ether for allergic patients. Theoretically, however, Cyclopropane® should be avoided in asthmatic patients because of its bronchoconstrictor effect. Allergic manifestations of the antigen-antibody type occur after repeated exposure to local anesthetic drugs. Undue reliance is placed upon skin tests for determining sensitivity to these materials. Skin testing procedures for a local anesthetic are of very little value. This author believes that intolerance may be detected by using the intranasal test, with an absence of blood pressure changes indicating that the patient is tolerant to the drug.

Since bronchospasm is a common characteristic of patients with pulmonary emphysema, nebulized epinephrine generally provides adequate treatment at the start of the disease. Barach[9] discusses the use of other bronchodilators. He considers one of the most important steps in emphysema is to stop the use of the bronchodilator drugs which the patient has been using and to substitute something else. It is important to recognize that retained secretions play a large role in evoking the symptoms of asthma and emphysema. Bronchodilator drugs may not be sufficient to assist in their removal. Manual compression of the thorax is additionally helpful. Diaphragmatic breathing is of utmost importance in the treatment of practically all patients with diseases of the chest. He considers exsufflation with negative pressure to be a valuable procedure in these patients.

Klinghoffer[88] reports a patient with the clinical picture compatible with Loeffler's syndrome following the vaginal installation of a sulfonamid cream. Recurrence was noted after each of three subsequent applications of the drug. No clinical manifestations followed the first use of the drug, but with each subsequent application there was progressive shortening of the time interval between the application and the appearance of symptoms. Skin tests were disappointing as an aid in diagnosis.

Benign transitory pulmonary infiltration with eosinophilia has been described by Mark.[105] Many of his patients had bronchospasm, with cough being the most frequent symptom. Elevated temperature was demonstrable in 50 per cent of the twenty-three cases studied by this author. Epinephrine gave little relief but blood transfusions rapidly cleared the lesions. Mark believes that allergy was not an important cause of Loeffler's syndrome.

Prickman and Peters[119] report a patient with allergic bronchial disease thought to be due to allergy to Cibalgine.® The complications of bronchostenosis, fever and bronchitis were thought to be infectious in nature superimposed upon the original allergic disease. Various forms of therapy were unsuccessful until the original cause—drug sensitivity—was recognized and eliminated. It is necessary in these instances to make an accurate diagnosis before successful treatment can be accomplished.

Postmortem examination reports on eighteen cases of bronchial asthma are made by Robertson and Sinclair.[123] Etiologic consideration revealed that psychologic, allergic and infective factors were present in the same patient at the same time. All cases had mucus plugging of the bronchi with tenacious mucus. These authors explained the sudden death in thirteen of the eighteen patients by a progressive rise in the intra-alveolar pressure which overcame the pulmonary capillary blood pressure. To assure good long-range results, Sheldon and his associates[135] advise environmental and dietary correction in the treatment of bronchial asthma. Intravenous or rectal administration of aminophyllin is of the greatest value for severe asthma, particularly in the aged patient. The management of infectious asthma is more difficult than the treatment of so-called atopic asthma. Appropriate antibiotic or chemotherapy should eradicate any bronchial infection that may be present. A thorough search for other sources of infection in the aged patient is necessary.

OTOLARYNGOLOGIC FINDINGS

Anderson and Rubin[3] describe some of the procedures used to enhance allergy management in the practice of otolaryngology. They feel that nose drops are not harmful if used in the proper amount or concentration and if therapy is not prolonged for a period of time. A prescription for nose drops in order to promote ventilation and drainage is of value in those allergic patients with superimposed infection of the nose, nasal pharynx and sinuses. It is more rational to administer an antibiotic preparation in a systemic manner rather than in form of nose drops. Bronchoscopy can prove to be of value to the allergist in many ways. These authors believe that the procedure is virtually neglected in the treatment of severe asthma. Bronchoscopy is a valuable aid in discovering the presence of complicating bronchiectasis either by direct inspection or by serving as a means for the installation of contrast media. It must be remembered that allergy is but one disorder that may interfere with the proper nasal function. The otolaryngologist is forced to conclude that his therapy must be directed against all factors, of which allergy is only one. If a normal air pattern can be established, the threshold of symptoms may be heightened so that the patient is apparently better able to tolerate exposure to previously offending allergens. Allergic management is the treatment of choice in the patient having nasal mucous polyps. Taub and Rosenberg[154] were able to obtain better results by these measures than with surgical removal. A thorough investigation to establish etiology, followed by an elimination program and specific desensitization procedures were the only measures employed. Seldom was it necessary to use any form of local therapy intranasally. McComiskey[99] believes that there is no substitute for complete surgical removal, down to the last vestige, of the attachment or root of a nasal polyp. This is true even if a radical ethmoidectomy has to be done. Allergy management and therapy should follow the surgical removal of polyps according to this author. Though there may be some reduction in the size of the nasal polyp, complete eradication with cortisone and allied compounds has

never been observed by this author. Recurrence of polypoid growth after the original growth and all visible roots had been removed may be accomplished with the insertion of radium in 100 mg capsules into the nose for a varying length of time. Harkins[69] also advises the surgical removal of nasal polyps. This is particularly true if they are obstructing the passages for comfortable breathing or preventing proper sinus aeration and drainage.

The clinical picture of allergy of the nose and paranasal sinuses is essentially the same in children as that seen in adults. Hampsey[68] believes that the "cold problem" of the allergic child is much improved by the adequate control of the allergic factor. Food sensitivity is important in many cases of allergic sinusitis in children. The most frequent causes, however, may be found in the inhalant group of allergens. The indications for tonsillectomy and adenoidectomy in the allergic child are stated to be essentially the same as those in the child who is not allergic. In preparing the allergic child for such surgery, adequate allergic management should be instituted prior to the operation. No nose and throat surgery should be performed during the pollen season if the patient is pollen-sensitive. The neglect of allergic management in the postoperative stage will permit a regrowth of lymphoid tissue in the nasopharynx or pharnyx.

AIR POLLUTION

Control of environmental inhalant allergy can be approached in a logical manner by cleaning the particulate matter from the indoor environmental air. Efficient mechanical devices based upon the principle of electrostatic precipitation are now widely utilized for the control of industrial dust and environmental problems. Friedlaender and Friedlaender[52] report their observations on the removal of pollen and the control of seasonal and nonseasonal allergic respiratory symptoms by a portable room-sized unit of inexpensive construction. The capacity of this unit is rated at 200 cubic feet per minute, being capable of circulating the air of a 2000 cubic foot room six times per hour. The precipitator was plugged into an ordinary electric outlet with this being the only requirement for installation. The efficiency of the machine is established when these authors report that pollen grains were removed from the air with 100 per cent efficiency. This type of electrostatic air cleaning was found to be very effective in certain asthmatic patients allergic to household dust.

The chief effects of air pollution were irritation of the upper respiratory tract and conjunctiva. An editorial[42] advises that residential districts should not be built in the direct line of the prevailing wind from a heavy can best be determined by studying their effects on a limited scale in industry. The maximum allowable concentrations of various pollutants can best be determined by studying their effects on a limited scale in industrial workers subject to daily exposure to polluted air. With good improvements in control and technological changes in industry, these community problems can be solved. There is no complete solution to the problem of air pollution, but measures can and should be undertaken, since it was demonstrated in several large cities that a control program was well worth while.

Schaffer and Seidmon[132] found fifty-one culturable fungi in their area over a twenty-month period. Air sampling was accomplished by the use of the Wells centrifuge. The peak of the fungi curve was in June and July with twelve fungi making up 90 percent of the total colonies recovered. These authors cultured thirty-three house dust samples and

thirty-seven of the fifty-one organisms found in the air were recovered. Forty-one of the fifty patients studied had symptoms during July and early August. It is during these months that the most important fungi are in the air in the greatest concentration. It is also at these times when the air is relatively free of timothy and ragweed pollen. In October, after the ragweed pollinating period is over, patients with symptoms were found to react to three or more of the important atmospheric fungi. In therapy, the addition of positive reactors to routine treatment schedules gave excellent results. They advocate the application of greater stress on the importance of fungi in inhalant seasonal allergy.

DRUG ALLERGY

Antihistaminic preparations have shown wide variation in their antipruritic effects. Cornia and Kuykendall[32] utilize the itch threshold to study the effects of various drugs on experimentally produced itching. Their criterion for the beneficial effects from the use of any local drug was the elevation of this threshold. Analgesic drugs, such as codeine and aspirin, had a better than average effect upon this experimental pruritus. Although sedation had an effect that was considered to be moderately beneficial, cortisone and calcium gluconate had little measurable effect upon itching.

Production of an asthmatic attack after inhalation of pituitary powder is the basis of an interesting case report by Hale.[65] Posterior pituitary powder by inhalation was used in treatment of diabetes insipidus. Because of the demonstrable sensitivity for this preparation, the patient avoided the use of the necessary drug unless he anticipated a situation that might be inconvenient or embarrassing. Hale found strongly positive scratch and intradermal cutaneous reactions to the posterior pituitary extract. Specific treatment, consisting of hypodermic administration of gradually increasing amounts of the crude posterior pituitary extract, was instituted and continued over a period of two years. The clinical sensitivity to pituitary preparations was definitely reduced, but there was little or no change in the degree of skin sensitivity. The author was able to demonstrate that the sensitization was specific for an antigen found in human pituitary as well as other mammalian pituitary glands.

Unsupervised treatment with a solution of potassium arsenite for a period of twenty-four days produced arsenic poisoning in the patient reported by Blumenthal.[16] Hepatitis, gastroenteritis, cardiac decompensation and dermatitis were the outstanding clinical signs and symptoms. The surprising feature of this serious complication was that the patient's symptoms of bronchial asthma were due to left ventricular heart failure rather than of allergic origin.

ACTH AND CORTISONE

Cortisone and corticotropin are exceedingly efficacious agents for the relief of symptomatic symptoms. It has been the subject of an editorial[43] that the benefits from these preparations are transitory and in no sense are the underlying state of hypersensitivity or the need for specific treatment altered in any way. The beneficial effects of these hormones in allergic diseases are derived from the creation of an artificial state of hyperadrenalism. There is no hormonal deficiency in those patients whose complaints are corrected by these preparations. It is quite fortunate that the dosage usually required to control allergic symptoms seldom produces serious effects during the first few weeks of treatment. Some of the

serious complications have an insidious onset and are not easily reversible. The activation of latent tuberculosis or peptic ulcer will often be a more difficult and dangerous problem than the disease for which the hormone was originally prescribed. Osteoporosis is one of the more recently recognized dangers of prolonged cortisone administration. In the presence of severe infection it is unwise to stop cortisone abruptly but safer to continue it with the use of appropriate antibiotics.

Hypersensitivity reactions have resulted from the use of corticotropin. Hill and Swinburn[73] have found these reactions range from urticaria to anaphylaxis. They feel that the reactions may be specific or nonspecific sensitivity to the protein material in the preparation. Addison's disease or a previous history of allergic reactions seem to favor the possibility of hypersensitivity with these agents. These authors report a patient in whom the initial symptoms of reaction occurred on the thirty-third day of treatment with intramuscular porcine corticotropin. Eventual death was stated to be due to anaphylactic shock, and the clinical findings were confirmed by necropsy. Though the patient had shown no previous reaction to pork or beef extracts with scratch tests intradermally, postmortem passive transfer reactions showed a slightly more increased reaction to the pork than to the beef corticotropin.

Unger and Unger[159] point out that serious untoward reactions can occur, especially swelling, increased blood pressure, glycosuria and reactivation of latent pulmonary tuberculosis and peptic ulcers. They recommend that allergic patients should have a complete allergy survey and time-tested allergic treatment prior to the use of either ACTH or cortisone. Continued use of ACTH is acceptable in the treatment of serum sickness, drug reactions, marked contact dermatitis (such as poison ivy), extremely severe bronchial asthma and severe or exfoliative dermatitis. These authors found that the use of these hormones was quite satisfactory in patients with respiratory type of allergic disease with less satisfactory results being noted in various types of dermatitis. The results in this latter group were temporary at best with definite relapse being noted with cessation of hormone treatment. Side-effects occurred in eleven of their eighty-five patients.

Swift's patient[151] showed positive skin test reactions to both beef and pork ACTH as well as a lesser reaction to the more highly purified gel preparation. A reaction to anterior pituitary extract was also determined. This patient had an anaphylactoid type reaction from ACTH administration. Passive transfer confirmation of these reactions was determined.

PENICILLIN

Rapid clearing of facial paralysis with cortisone therapy was reported by Halpin.[67] His patient had received both penicillin and antitetanus serum shortly before the onset of a typical Bell's palsy. The initial symptoms of reaction were noted about three days after the administration of these preparations, with the onset of the facial paralysis occurring approximately twenty days after the serum and penicillin administration. Rapid clearing of this facial paralysis was noted and complete recovery was prompt compared to the notoriously prolonged persistent paralysis usually seen in these instances. It was highly suggestive that the Bell's palsy was the result of sensitivity to either serum or penicillin.

Kern and Wimberley[84] reported that fifteen deaths from penicillin were noted in the literature during the eighteen months preceding their paper.

The alarming frequency with which fatal reactions occurred led them to suggest that perhaps many insidious reactions were not being reported as anaphylactic death from this drug. Circulating antibodies are demonstrable only in the most severe type of drug reactions. The authors advise that allergic patients, even without previous history of penicillin sensitivity, should always be tested intracutaneously prior to the administration of this drug. Mild reactions are usually noted in those patients who show delayed skin test type reactions, and these patients seldom develop serious trouble. Kern and Wimberley call attention to the fact that a negative skin test reaction does not rule out sensitivity, but it does confirm the probability that any reaction will not be severe. They warn against the combination of penicillin with any other drug—such as Neo-Penil®—when giving it parenterally, because these preparations seem to cause more serious type of reaction.

Electrocardiographic findings indicative of pericarditis were observed in a patient suffering a penicillin reaction. Glotzer[58] found that these electrocardiographic changes were still abnormal four days after the original reading. Return to normal required ten days. Inversion of T waves in all limb and chest leads with a flattened T in lead AVl were the main findings. Slight heart enlargement with a slightly enlarged and tender liver were outstanding findings among the other characteristic signs and symptoms of a penicillin reaction. The drug, in this instance, had been administered by the oral route.

Clinical toxicity of antibiotics and sulfonamides is the subject of an interesting survey of the literature by Kutscher, Lane and Segall.[91] Their table summarized nearly all of the large clinical studies involving most antibiotics and sulfonamid preparations. The attention of the interested reader is drawn to this article.

The effect of drug toxicity in bio-assay must be considered in relation to the whole patient. Brown[19] feels that the problem of bio-assay of antibiotic agents needs an entirely new approach. We must consider their mechanism of action, toxicity, allergenicity and the limitations of *in vitro*, animal *in vivo* and human *in vivo* studies. The changing disease process and changing bacteria must be taken into consideration.

Madalin[102] has reported a patient who experienced an anaphylactoid reaction following the use of a penicillin lozenge. About two minutes after she had placed the medication in her mouth, she began to vomit and became unconscious. Unconsciousness continued for a period of about two hours with relief being obtained by intravenous 5 per cent glucose and nasal oxygen. Subsequently, she experienced a comparatively mild reaction to an injection of penicillin and another antibiotic when taken by mouth. Intradermal testing with the various forms of penicillin produced mild episodes of shock when the pseudopods reached their maximum level.

Very few instances of anaphylaxis resulting from the topical administration of penicillin have been reported. Carter and Cope[25] describe a patient who had received a long course of penicillin therapy in treatment of syphilis. She had received 4,800,000 units of penicillin over a fifteen-day period in 1946 without any noticeable side-effects. Tightness in the chest and wheezing were experienced following an injection of penicillin in 1953. Later in that same year this patient applied penicillin ophthalmic ointment to her right eye and within seconds developed an offensive taste in her mouth. This was followed very shortly by shortness of breath, a flushed appearance, lower abdominal cramping and marked diarrhea.

There was no loss of consciousness, and the patient was returned to normal status within about one hour. Positive patch test reactions were obtained with penicillin ophthalmic ointment; but to the nonpenicillin-containing base, which served as a control, there was no immediate nor delayed reaction.

Some of these cutaneous drug reactions may not be due to allergy. Rostenberg and Webster[127] emphasize the diversity of means by which skin reactions can be produced. Normal pharmacologic effects of the drug are often identified as so-called side reactions or reactions. The administration of antibiotic preparations should have definite indications, according to Fisher.[49] He has reported an anaphylactic death of a patient who died within minutes after receiving intramuscular penicillin subsequent to an apparently minor operation. Necropsy findings in the brain showed considerable congestion and edema with these changes also present in the cerebral cortex, basal ganglia, medulla, pons and cerebellum. Penicillin sensitivity has been stated to be much less in children than in adults. This would seem to be confirmed by the report of Collins-Williams and Vincent.[30] In their hospital with 18,000 inpatient and 83,000 outpatient admissions, they were able to observe only three definite penicillin reactions. They reported no cases of anaphylactic shock in this pediatric hospital. These authors believe that skin testing is of little value as a reliable method of detecting penicillin sensitivity and recommend more reliance to be placed upon a carefully taken history.

Another fatality following injection of penicillin has been reported by Bell.[12] This patient had received crystalline penicillin twice daily for several days following a minor operation. Ten days later he was reoperated, and penicillin therapy was given again. The patient remained perfectly well until about two weeks following the first operation when he was given an initial injection of procaine penicillin, which was followed immediately by generalized pain, pallor and deep cyanosis. Pulmonary edema was marked, and in spite of emergency measures the patient expired within a few minutes after this injection. Curphey[33] reports two patients who had anaphylactic type deaths following the administration of penicillin. Both patients at autopsy had bronchi which showed acutely congested mucosal surfaces with the lumina filled with mucus containing many eosinophils. Infiltration of round cells and eosinophils into the bronchial walls and peribronchial tissue was present in both instances. His patients were given penicillin for treatment of purulent, posterior nasal drip and pharyngeal infection in one instance and for the treatment of an asthmatic attack in the other. Absence of an eosinophilic response in the lung tissues and in bronchial secretions was the outstanding finding at necropsy of the patient reported by Etter and Merryman.[46] They believe that the immediate anaphylactic reaction was so rapid that the usual eosinophilic response was not seen. Though they could determine no evidence of accidental intravenous injection of penicillin procaine, they considered this possibility. Anaphylactic death following the administration of repository penicillin is reported by Goldman.[60] His patient had received approximately fifteen injections of procaine penicillin during the three and one-half years preceding his fatality. Speculation is made as to whether the patient was sensitive to the entire molecular composite that had been given or whether the patient was sensitive only to the penicillin complex. This was considered to be the first fatality due to dipenicillin G.

This reviewer is familiar with another unreported case of fatality due

to penicillin administration. The patient had had a long history of bronchial asthma with complicating bronchiectasis. Repeated attacks of severe asthma, elevated temperature, marked purulent sputum and obvious distress were readily relieved with hospitalization, the administration of penicillin and bronchodilator medications. This procedure was necessary at intervals of about every two months throughout the year. No reactions were experienced over a period of two to three years. The patient then moved from the middle west to the southwestern part of the United States with a transcript of her clinical record being forwarded to the physician to whom she was referred in that area. The measures described in the above few sentences were used on one occasion with no untoward reaction. With the onset of a subsequent typical attack of these same symptoms, the administration of penicillin caused immediate and violent death within a matter of two to three minutes. I do not mean to be facetious when I say that this physician and I were deeply apologetic to each other on the first occasion that we met after this unfortunate incident. He was sorry for having "caused" the death of the patient; and I, in the same breath was sorry for putting him on such an unpleasant and unfortunate spot.

Jennings and Olansky[79] studied the determination of the effectiveness of Pronestyl in the treatment of penicillin reactions. Its effectiveness in preventing such reactions was also a part of this study. Of twenty-four patients treated with procaine amide (Pronestyl®), twenty-two were in the excellent or good category; and no patient responded poorly. Eleven of seventeen patients showed excellent or good response to Benadryl® when used in the treatment of penicillin reaction. These authors believe that Pronestyl is not the final answer to the treatment of penicillin reaction; but they do believe that this drug proved to be at least as good, and probably better than, Benadryl for this purpose. Because Pronestyl was found to afford rapid relief of symptoms in many of these penicillin reactions, the authors state (surprisingly!) that ACTH and cortisone are unnecessary in the average penicillin reaction. They apparently believe that these hormones should be reserved for only the severe reaction that might lead to fatality. Pronestyl appeared to be useful in the prevention of allergic reactions in those persons who were known reactors to the drug. All the eighteen patients studied in this category were able to complete a course of penicillin without reaction. Reactions that did develop in three of four patients were present after the drug had been stopped.

PIROMEN®

Aronoff and Ghaemi[4] used Piromen® in drug eruptions, contact dermatitis, dermatitis venenata, urticaria, bronchial asthma, hay fever, vasomotor rhinitis, serum reactions and other forms of demonstrable allergy. Good results were reported in fifty-seven of seventy-one cases in all groups. They recommend the intravenous route of drug administration because of a better response. Combination of proper allergic management with Piromen therapy was most beneficial in respiratory and dermatologic cases. They do not believe that hyperpyrexia is necessary although the production of constitutional symptoms did seem to be associated with the appearance of beneficial results in some patients. The dosage level in their cases ranged from four to seven gamma or less. They believe that this drug is a safe one to use with only a few patients showing any side effects of note.

Since hypophysectomized animals do not respond to Piromen, Randolph[120] believes that the action of Piromen involves the anterior pituitary with secondary adrenal effects. Stimulation of the adrenal cortex and changes with cellular responses are the two major pharmacodynamic effects. He employs Piromen therapy as an adjunctive nonspecific treatment in chronic allergic conditions. Administration of this preparation may be given by the intravenous or subcutaneous route; once beneficial effects have been established, maintenance of these effects may be continued by the use of sublingual dosages. He states that Piromen's field of greatest usefulness lies in the direction of supplementing specific therapy in the treatment of difficult allergic states. This is particularly of value, according to this author, in those patients with multiple sensitivities.

Knight[89] used Piromen alone in thirty-nine cases and added this to prior therapy in thirty-one additional patients. Duration of treatment varied from three days to twenty-two months, with the minimum period being three weeks. Improvement, if it were going to occur, usually appeared before the sixth injection. Slightly more than half his cases obtained definite amelioration of symptoms. In about one-fifth of the total, relief was very satisfactory. In those cases showing improvement, there was no obvious change in circulating eosinophils. Knight believes that it is obvious that Piromen is not the long sought panacea for the treatment of allergic disorders, and he does not recommend it as a substitute for routine allergic management. Pounders[118] was disappointed in the results with Piromen in the treatment of atopic dermatitis.

MISCELLANEOUS DRUGS

It is necessary to differentiate arthralgia developing during hydralazine therapy from other syndromes. Slonim[142] gave definite relief to a reaction from this preparation by the use of cortisone. Subsequent administration of hydralazine (Apresoline®) produced a recurrence of these original symptoms of arthralgia, headache, prostration, skin lesions and glossodynia. Aplastic anemia was present in twenty-eight of thirty-one cases of blood dyscrasias associated with chloramphenicol therapy. Hodgkinson[75] reported that all except two of these patients showed some bleeding manifestations. Jaundice was present in eight patients and appeared between the time of administration of the drug and the onset of the blood dyscrasias. Twenty-four of these thirty-one reported cases expired, and three were being sustained by blood transfusions. The total dosage of chloramphenicol for adults should not exceed twenty-six grams, and in children the dosage should not be more than 100 mg per kilogram of body weight daily for seven days. The over-all length of treatment with this drug should not exceed ten days.

Makous and Vander Veer[103] describe a patient with thrombophlebitis who was treated with phenindione (Phenylindandione). Symptoms of general reaction appeared with the main characteristics being hepatitis, jaundice, skin rash, anemia and a leukomoid blood picture. The skin test for reaction to phenindione was positive though not strikingly so. Passive transfer skin tests were unsuccessful. A febrile and systemic response with this drug resulted from an oral provocative test. They feel that the severity of the reaction in this patient may have been due to the fact that therapy was reinaugurated during the initial phase of the sensitivity reaction and that during the first twenty-four hours the patient received 14 mg per kilogram of body weight of phenindione.

Korst[90] describes a patient representing a severe allergic reaction to para-aminosalicylic acid. The reaction was thought to be specific for this drug inasmuch as the patient had no allergic history. There was no evident reaction to other medications. The drug had been given to the patient for twenty-eight days prior to the reaction. Had the complaints been due to drug toxicity, it was expected that the symptoms would have been manifested at an earlier date. Most severe PAS reactions seem to be of the acquired sensitivity type. It is important to recognize reactions to this drug because of the increasing use of PAS in the chemotherapy of tuberculosis. The reaction is characterized by fever, rash, nausea, vomiting, aching and pain in the joints, headache and sometimes mild paresthesias. Eosinophilia is a frequent finding. None of the reported reactions have been fatal, with the reaction subsiding promptly when the drug is stopped. Though the history of allergy to other types of drugs or a history of drug intolerance does not necessarily indicate that the acquired sensitivity will develop for PAS, reactions can be expected within the first six or seven weeks of therapy. It is important to check for cross-sensitivity to salicylates in sensitive patients. A test dose of the drug, given orally, seems to be the most definite means of identifying PAS as the drug at fault when sensitivity is suspected.

Control of postoperative nausea and vomiting with Benadryl® is the subject of a report by Warrington, Pasquesi, Kulasavage and McCawley.[162] The incidence of this unpleasant finding was reduced from 50 per cent in the control series to 5 per cent in those patients to whom the antihistaminic preparation had been administered intravenously in a dosage of 100 mg. Smaller doses of this drug seemed to be less effective in producing beneficial results. Relief was obtained in eighteen of twenty-five episodes of vomiting of varying etiology. Striking relief in radiation sickness has been provided by chlorpromazine. Chinn and Sheldon[27] were able to protect dogs from vomiting after 800 r x-radiation with a dosage of 10 mg per kilogram of body weight. Injections of half this dosage were ineffective. These authors warn that the previous reports of stability for twenty-four hours are not in agreement with their findings that ineffective results were obtained with solutions of this drug allowed to stand for two hours. In spite of the good effects reported from the intravenous use of Benadryl in the control of nausea, it seems that chlorpromazine is the drug of choice in this condition. Mark[105] obtained moderate to complete relief in post-x-ray nausea when giving thorazine orally in a dosage of 10 to 25 mg three times daily in eighty of eighty-four patients. The nausea and vomiting associated with migraine headache was well controlled with this drug. An anti-emetic effect in morning nausea of pregnancy and in postoperative patients was observed. The use of chlorpromazine in status asthmaticus was suggested by the pharmacology of this drug. Intravenous administration to four patients reported by Robinson and Zuck.[124] The patients were able to sleep without experiencing respiratory depression, and their asthma was somewhat relieved. The patients obtained satisfactory rest on this preparation. Parenteral chlorpromazine therapy should be reserved for severe cases of status asthmaticus that are unresponsive to antispasmodic drugs. Oral administration of the preparation gives relief in only mild cases with the parenteral administration of chlorpromazine being reserved for the severe patients.

DERMATOLOGY

Acne vulgaris is said to be a physiologic occurrence during adolescence. X-ray therapy has been widely employed in resistant cases of acne vulgaris even though most of these treated patients will show a high incidence of relapse. Rubin[131] has stated that x-ray treatment for acne in patients who are less than seventeen years of age should not be advised. Estrogens have been used more widely in recent years for treatment of acne than almost any other form of therapy. Oral estrogens should not be administered in an effort to influence skin metabolism unless there is some history in women of menstrual irregularity and in men where there is some evidence of estrogen deficiency. Shapiro[133] has shown that topically applied estrogen exerts the desired effect at the desired site. His present study is concerned with a small group of patients with chronic cystic and pustular relapsing acne. To avoid those patients who might have natural spontaneous remissions he chose his patients from a group with the following reservations: complaints of acne for a period of five years duration, a history of relapse after x-ray, Alpine rays and vaccine therapy and patients who were in good general health with no apparent metabolic dysfunctions. A remission in refractory, chronic, severe acne could be induced in six weeks in approximately 70 per cent of the patients by an application of 1 cc of a special Premarin® lotion twice daily. This lotion contains 1.0 milligram of conjugated estrogens in each cubic centimeter. With this local application the flexibility of dosage control is very evident. There are no unwarranted side-effects with a correctly adjusted dosage schedule.

Oral procaine has been effective in penicillin urticaria, herpes zoster and burning tongue as reported by Beinhauer.[11] Procaine hydrochloride was combined with ascorbic acid and given orally to 145 patients. Relief from itching was apparent within four days in a great number of patients. Complete relief, however, was experienced in only 22 per cent with failures in 49 per cent. For pruritus ani, Becker[10] found that topical cortisone acetate was the most effective form of treatment yet discovered. Complete relief is obtained with application of this preparation twice daily. The frequency of application is then reduced to once daily, and treatment is eventually discontinued when the skin appears to be normal.

PATCH TESTING

A buffered aluminum acetate cream aids in the alkaline neutralization ability of the skin. Gross and his co-workers[63] state that it is this latter impairment which produces "housewives' eczema." No reactions of sensitivity were experienced to this preparation. An impressive proportion of all dermatologic cases will be hand dermatitis. Brunner[21] found his patients to have a varied etiologic background, but external irritation from cleansing agents seemed to be of primary importance. One hundred eight of 145 cases of nonspecific eczematous dermatitis of the hands were in housewives. Clearing was noticed in a period from four weeks to three months. Though synthetic detergents used in housework may irritate the skin it cannot be assumed that such detergents are the only causes for dermatitis of the hands in housewives. A successful regimen is one in which strict avoidance of external irritations is accomplished, with soothing nonirritating topical therapy being added as an adjunctive. Recurrences are quite common and seem to be aggravated by water and other materials which cause the hands to be continually wet.

The cause in many cases of contact dermatitis can be determined with diagnostic patch testing when this procedure is properly performed and correctly interpreted. A committee report[81] reveals that the use of and dependency on this test must be based upon the clinical history, the nature of the lesions, the site of the eruption and the course of the disease. Proper concentration of the test material is of utmost importance. The eczematized skin, as seen in chronic contact dermatitis, has a much lower threshold of reactivity of specific and nonspecific nature than does the normal skin. A highly effective patch test must be confirmed in its positive reactions by trial and error and usage. It is not justifiable to place absolute reliance upon the results of patch testing in all cases of contact-type dermatitis. An important part of the etiologic background in hand eczema is metal sensitivity, according to Gaul.[54] He found no evidence of cross-sensitization between metals and their salts. Though a positive patch test may be considered as an important finding, it should never be construed as solving the etiology in any given case of hand eczema. It is necessary to differentiate between a traumatic type of reaction and a true reaction of sensitivity when doing patch testing. A true positive patch test will produce itching at the site of application. Edema, papules and vesicles will be noted. In these patients with suspected sensitivity to metal, Gaul felt that the patch test must necessarily remain positive for one week to be considered as definitely important.

Contact dermatitis of the feet due to shoes may closely resemble dermatophytosis. Shatin and Reisch[134] have found that the anterodorsal portion of the foot is most commonly involved, with the lesion usually beginning on the dorsal surface of the big toe. Erythema, scaling, vesiculation and other evidence of inflammation are originally noticed. The most common offending material in shoe dermatitis is the thermoplastic material used in the boxed toes of shoes. They found no correlation between the length of time the shoes were worn and the onset of the dermatitis. Excessive sweating of the feet or wetting of the shoes by rain or snow were exacerbating or initiating factors.

Fisher[48] emphasizes that the clearing of stomatitis when a denture is not worn and the prompt recurrence of a sore mouth with the use of the plate is no proof of allergic sensitization to the denture. He considers pressure and trauma of an ill-fitting plate to result in the same symptom complex. He reports a series of patients with sore mouths caused by dentures. None of these were allergic to the completely polymerized acrylic denture. Patch testing by strapping the entire plate to the forearm may lead to many diagnostic errors since redness, papulation, vesiculation and even bulla formation may result from nonspecific pressure effects. These may readily be confused with true allergic reactions. Patch testing with the liquid monomer alone is sufficient to indicate the presence or absence of allergic sensitization to acrylic denture material. The polymer and the heat cured plate have not been shown to be sensitizers.

ATOPIC ECZEMA AND URTICARIA

Staphylococcus toxoid, ACTH and cortisone were worthwhile remedies in atopic dermatitis, according to Pounders.[118] Smaller dosages of cortisone were employed by this author in the treatment of these patients with skin lesions than is usually suggested for other conditions. He uses cortisone, however, to give a moderate degree of relief and not to entirely clear up the symptoms. Overall[111] advises against the

overtreatment of any atopic eczema. Careful treatment may forestall what this author calls the dermo-respiratory syndrome. Wet dressings are the treatment of choice in the early weeping acute stage. Scratching must be prevented. Cortisone or hydrocortisone, orally or by local application, may occasionally be necessary; but they should not be used as the treatment of choice. Dietary management, sedatives—both for the child patient and occasionally for the worried mother—and antihistamines will be a source of relief. Oral therapy includes the automatic elimination of milk, wheat and egg from the diet of the patient.

Stoesser and Nelson[147] suggest that the routine use of a soy bean preparation in all cases of infantile eczema is not a satisfactory procedure. Some of their patients appeared to improve and others failed to respond. The children who do well are found, in many instances, to be definitely allergic to milk either by trial diet or by positive skin tests. These authors consider two forms of infantile eczema which they describe as allergic dermatitis and atopic erythroderma. Topical therapy must be carried out for each type in a more or less routine manner. In those patients with allergic dermatitis, the replacement of milk with a soy bean preparation gave a satisfactory response. The authors consider that some of their patients had additional help from the high content of unsaturated fatty acids in the soy oil. The infants with a diagnosis of atopic erythroderma, in whom soy bean products were used as a milk substitute, derived no definite benefit from this dietary management.

Epidermal reaction is found in dermatitis caused by external contact. The type of reaction is almost identical whether the dermatitis is due to a primary irritant or to a substance to which the individual has become sensitized. Pinkus[116] states that the first visible change in the skin is alteration of individual prickle cells and intercellular edema. This leads to the formation of a vesicle when the damaged cell is dissolved. He reports that the acute urticarial wheal is characterized by dilatation of capillaries, exudation of fluid through the vascular wall and accumulation of eosinophils in the perivascular tissue. The tissue reaction based on tuberculin-type response has manifestations found in chronic granulomatous inflammation. The tissue response and clinical picture of the human skin can vary in great degree. The number and virulence of the invading organism, the route by which it reaches the skin and the exact site at which it localizes, all play their part in determining the eventual result.

Siegel and Bergeron[140] tried to correlate the role of infection, both acute and chronic, as causative factors of urticaria and angioedema. In their series of 115 patients infection played a major role in the production of the urticaria. It is conceivable that an antigen-antibody reaction is present in this type of instance. They found no electrocardiographic changes in ninety-eight patients studied with cardiac abnormalities. This would indicate that cardiac abnormalities, described with serum sickness, urticaria and similar hypersensitivity reactions, are probably rare. They were unable to determine the etiology in 31 per cent of the patients studied. In an all-inclusive survey of 500 cases, Steinhardt[146] reported that urticaria is more common in the twenty to forty age group. Females were seen more frequently with urticaria than were males. This is perhaps explained by the prevalent use of medications during the child-bearing age and to a greater incidence of pelvis infections and endocrine imbalance. Steinhardt suggests that skin tests are of little help in determining the etiology of urticaria and angioedema. The eosinophil count is not an absolute diagnostic aid and often may be misleading. The pruritus in

78 per cent of his patients was relieved with antihistamines. Ideal therapy is initiated with a search for the etiologic factor and its eventual elimination. Though the diagnosis of urticaria and angioedema is a simple procedure, Sheldon, Mathews and Lovell[136] call these problems "vexing." How true they are! The management of these patients is indeed a formidable task. A thorough history is the most important initial step in evaluating the cause of urticaria. Experience has shown that drug allergy, food allergy, infection and psychic factors are the most common apparent causes. These authors have reviewed the literature since 1945 in an attempt to find new, helpful information which might be of assistance in the evaluation of the more difficult cases.

Ingels[77] has reported good results in the treatment of psoriasis with the use of pancreatic extracts. Twenty-four patients were treated with this preparation only, and the condition showed good response in four patients after four weeks of therapy. After longer periods of treatment a good response was observed in fifteen other cases. Few undesirable side effects were noted for the use of this enteric coated pancreatic extract. His results, however, are not conclusive in view of the fact that psoriasis is often influenced by psychic factors or by spontaneous improvement.

To the dermatologist, fungi are quite as important as bacteria. An all-inclusive discussion of the dermatophytes[143] will provide an interesting evening of study and observation.

Baird[7] states that it is reasonable to suspect hypersensitivity to bacteria as an etiologic factor in many so-called skin diseases. For the past several years he has been treating skin reactions which could be due to bacterial allergy by a combination of bacterial antigen and antibody. Though this method is not a specific, it represents a means of altering the patient's type of reaction. In this manner it seems to reach the fundamental causes of many cases of skin diseases. Baird reports 90 per cent success in eighty-four cases of eczema and in fifty-seven cases of erythematous and papular rashes. Dosages have been quite small. It is absolutely important to give the inoculation subcutaneously rather than intramuscularly, in the opinion of this author. Severe reactions have been exceedingly rare and never serious; though occasional side-reactions of chilliness, elevated temperature or slight nausea may occur.

Foster[51] has stated the pH determinations on the skin of 135 patients with generalized neurodermatitis averaged 6.35. The average pH was 5.4 on 138 patients with lesions other than neurodermatitis. When they were placed upon an "acid regime," the skin pH in these patients with neurodermatitis decreased an average of 0.43. The "acid regime" consists of the ingestion of dilute hydrochloric acid and a diet which consistently produces an acid urine. The results, however, were not too startling, as only thirty patients became clinically well while others were reported as "nearly well" and "improved."

HYDROCORTISONE OINTMENTS

Forbes[50] studied 126 patients with cutaneous bacterial infections. One hundred nine responded satisfactorily in seven days or less when Neomycin lotion was used. No instances of sensitization or primary irritation were seen in any of these patients. He concludes that Neomycin lotion is an effective agent in the treatment of cutaneous bacterial infections and is of particular value where skin lesions are due to hemolytic staphylococci. Kile[86] found that hydrocortisone-Neomycin ointment was a very effective tool in certain skin conditions. His clinical study of one hunderd patients

with various skin problems showed the most dramatic results in patch vesicular dermatitis that occurs on the hands. Two of his patients were sensitive to hydrocortisone and developed a definite flare at the points of its application. Sulzberger and Witten[149] observed 75 to 90 per cent improvement at the end of the first week of treatment with hydrocortisone ointment. Only rarely did favorable response follow an initial lag period of a few days to two weeks. Once a satisfactory response had been achieved, the continued use of hydrocortisone ointment maintained the improvement. Two applications a day of this preparation were usually sufficient when starting treatment, although three applications a day were sometimes required to achieve adequate relief. The frequency of applications may be decreased once the maximal degree of improvement has been reached. The optimal strength of the ointment seemed to be 2.5 per cent. Concentrations greater than this did not cause an appreciable increase in the efficacy of the ointment. In no instance did the topical application of hydrocortisone ointment produce adverse systemic effects. In some cases, these authors found that the continued topical use of hydrocortisone was as effective as the oral administration of the hormone. These same authors[150] report on thirty-five patients to whom oral administration of cortisone was given over a prolonged period of time in treatment of a variety of dermatoses. It was most encouraging to find that, in their experience with prolonged administration of cortisone, they were able gradually to reduce the amount of the hormone given each day. The maintenance dosage often was only a fraction of the original amount required to control the disease. In differentiating between addiction and dependence as applied to the oral use of cortisone, no evidence has been revealed to substantiate true addiction to the drug. Relief and comfort can be extended to patients suffering from ordinarily incapacitating skin diseases, and the life of patients with dermatoses ordinarily considered fatal can be prolonged.

Topical hydrocortisone was used in the treatment of seventy-nine patients with poison ivy dermatitis by Eskind and his co-workers.[45] Their findings showed that in most instances hydrocortisone applications were valueless, and slightly better results were obtained with placebo applications. Goldman and Preston[59] found that oral hydrocortisone was more effective than oral cortisone. Their work also demonstrated the effectiveness of hydrocortisone ointments in poison ivy dermatitis. This is in complete disagreement with the above report. Goldman and Preston prefer the lanolin base hydrocortisone ointment since it is more effective locally than is the hormone in other bases. A good response was obtained from the use of hydrocortisone ointment in about 67 per cent of the cases of infantile eczema reported by Witten, Amler, Salzberger and DeSanctis.[165] Initial improvement was noted within twenty-four to forty-eight hours after the first application of the preparation. In this study the authors placed the hormone ointment on one extremity or one side of the body and the control ointment was placed on the contra-lateral areas. In no instance did they find intolerance to the medication, and at no time was it necessary to suspect the ointment as a cause of irritation or sensitization. These authors consider hydrocortisone ointment to be the most effective, simplest and cleanest topical form of treatment of infantile eczema. A similar study has been reported by McCorriston.[100] His results were similar to the above report, with the added statement that 2.5 per cent ointment was more effective than the 1 per cent concentration. In 60 per cent of the 104 children studied, the improvement obtained with this form of topical medication was maintained after the therapy was discontinued.

GASTROINTESTINAL

Unusual reactions upon eating certain foods may be caused by psychogenic or allergenic mechanisms. The relative importance of each of these factors is discussed by Kaufman.[83] Fixed food allergy is relatively uncommon, but variable food allergy is quite common although little is known about this latter classification. There are certain characteristics regarding allergic reactions to food that should be emphasized: (1) A latent period between ingestion of the food and the appearance of signs and symptoms is usually noted. (2) The allergic syndrome has a particular pattern of development and regression. This author states that some patients will have conscious or unconscious needs to eat foods which they know will make them ill. Self-inflicted food-induced allergy can become a recurrent problem if the patient is unable to make an adequate adjustment. Patients with food allergies require the assistance of expert psychotherapy as well as expert allergic therapy.

Epigastric symptoms relieved by elimination diets are best explained by gastric allergy and allergic reactivity in the peritoneum. Rowe, Rowe and Uyeyama[130] report that this epigastric syndrome is characterized by pressure, fullness, burning, soreness, aching and pain in varying degrees. The diet history in these instances will reveal suspected sensitivity for foods present in 56 per cent of the cases. Less frequently dislikes for foods, especially for milk, will be observed. Because of the fallibility of skin tests with food extracts, diet trial has been used to study possible food allergy. Surgical removal of gall stones in one instance did not relieve the epigastric syndrome until proper anti-allergic diet was prescribed. The evident cause of the epigastric syndrome is stated to be food allergy. It is necessary to assume a maximum degree of allergy to excluded foods while possible food allergy is being studied. Rowe[128] uses trial diets as diagnostic tools. The accurate use of elimination diets not only reveals, but also may exclude, food allergy in any particular patient.

ULCERATIVE COLITIS

Cohen and Stapinski[28] report an instance in which urticaria and diarrhea were thought to be due to the parasite, *Trichomonas hominis*. Within one to two days after completion of therapy for the removal of the parasite, diarrhea and urticaria were practically completely cleared. The therapeutic agent here was Aureomycin,® 500 mg orally every six hours for four days. In patients with chronic ulcerative colitis, pollen allergy alone or associated with food allergy may produce an exaggeration of symptoms during the pollen season. Rowe and Rowe[129] were able to relieve some of these diagnostic problems by pollen therapy. In a review of their patients, ulcerative colitis was due to food allergy alone in 45 per cent and associated with pollen allergy in 10 per cent. Food allergy was determined in 70 per cent of their patients. Excellent results were obtained in 45 per cent with anti-allergic therapy either with or without adjunctive treatment.

A study of 120 patients with ulcerative colitis is reported by Kirsner and Palmer.[87] It is interesting to note that hay fever and asthma were present in nineteen of these patients, and a family history of hay fever and asthma was elicited in an additional thirteen. Emotional disturbances were recognized in 105 of the 120 cases. The clinical response to corticotropin was estimated as good in seventy patients, moderately favorable in twenty-four, slight in seven and none in three. The beneficial effect was characterized by prompt disappearance of elevated temperature, tachycardia, abdominal distress and bloody diarrhea. Increased appetite and a feeling of well-being

were favorable features. Proctoscopic examination revealed definite improvement in the appearance of the bowel in the majority of patients. Hormone therapy produced no demonstrable change in polyps or rectal strictures when present in these patients. A favorable clinical response in 103 of the 120 patients is reported by Skinner.[141] Allergic factors are mentioned as possible etiologic characteristics of ulcerative colitis. He thought that milk, egg, wheat, potato, orange and tomato might be causative factors. The suggestion is made that inhalants, particularly pollen, might aggravate the bowel condition.

Martin[108] has been impressed by the frequence with which a positive family history for allergy is elicited in many cases of colic. He found that 60 per cent of colic was in allergic families. This was much higher than the over-all incidence of those patients interviewed. He is dissatisfied with his form of treatment. His therapeutic program places the newborn child on a soy bean formula and synthetic vitamins if the parents have major allergic backgrounds. Sedation of these infants is an important part in giving them temporary relief and a definite smooth muscle antispasmodic should be provided. When the colic is under control, the sedative is the first thing removed from the therapeutic program. The wise therapeutic program for the baby with colic will consider allergy to be an important cause of the complaints.

CELIAC DISEASE

The diagnosis of celiac disease can be made when the following criteria are satisfied: failure to thrive, abnormal undigested stools, enlarged abdomen and a reduced glucose tolerance and vitamin A absorption. Collins-Williams and Ebbs[29] studied the correlation between skin test reactions and clinical experience. They tested twenty-eight patients with forty-seven of the common foods. All tests were done by the intracutaneous method with a full realization of the limitations of skin testing with foods. Examination of the results of the skin test at once shows that there is very little correlation between the tests and the clinical results. Wheat gave a positive reaction as often as any other food with the exception of egg. However, it gave this reaction in only six of the twenty-eight cases; and wheat fractions gave positive reactions in four additional cases. Therefore, ten cases gave positive reactions to wheat or its fractions while eighteen gave negative reactions. Seventeen of the twenty-eight patients had a family history of major allergy, but only five patients suffered from a major allergy themselves. When a diagnosis of celiac syndrome due to gastrointestinal allergy has been established, skin testing is of very little value in determining the causative foods.

Auman and Menzel[5] analyzed 143 food extracts for both protein nitrogen and total nitrogen. The ratio of protein nitrogen and total nitrogen values varied considerably in different preparations of the same extract. These authors recommend that food extracts should be standardized on a protein nitrogen basis in the same manner as pollen and inhalant extracts. They could find no regular correlation to exist between protein nitrogen and total nitrogen values for food extracts.

HEADACHES

The most frequently encountered headaches are vascular and of the migraine type. Sustained contractions of skeletal muscle about the face, scalp and neck are associated with these headaches.

Tunis and Wolff[158] state that headache is almost invariably associated

with disturbances of function in this tissue within or adjacent to the cranium. Seldom is there any reference of pain to a remote part of the body when the patient is suffering with pain in the head. Vascular headaches are associated with dilatation and distention of certain cranial arteries. Three groups can be discerned. Vascular headache of the migraine type is periodic. Anorexia, nausea or vomiting and mood disturbances may precede or accompany the headache. A family history of vascular headache in these patients is very common. The second group is made up of typical facial neuralgia and analogous vascular, cranial, facial pain syndromes. The location, duration and intensity of the pain is usually associated with painful dilatation and distention of the external carotid artery. Typically there is recurrent unilateral pain continuous for intervals from a few minutes to several days. Most of these patients are females between the ages of thirty and fifty years of age. The third classification of vascular headache occurs at the back of the head and neck and is called "occipital neuralgia." This headache is throbbing, worse on lying down, and is of two to thirty-six hours duration.

In general, the incidence of headache is recorded at about 8 per cent of the population. Vascular headaches are usually characterized by throbbing and pulsating head pain. In some headaches, patients will obtain relief in a prone position whereas other headaches are aggravated by this position. A detailed history with a description of the attack as to its onset, location and accompanying symptoms is all-important in making an accurate diagnosis. The emotional status must be carefully evaluated, for emotional stress is a dominant factor in tension headache and migraine patients. This reviewer feels that allergy investigative procedures are of little help in finding the allergic cause of attack. As yet no cure for migraine has been discovered, and the headache problem remains a challenge (and a headache) to most physicians. Chambers[26] reports that allergy constitutes only about 4 per cent of the factors producing headaches. Allergic headache is stated to be unilateral, excruciating, of short duration and often associated with stuffiness of the nose and tearing of the eyes. Excessive dilatation of extracranial arteries or excessive tension in the muscles of the head and neck are the two major mechanisms of headache, according to Lovshin.[96] He considers headache to be a disease of civilization and stress along with peptic ulcer. In the seven presented cases many tensions, frustrations and personality difficulties were disclosed. These seven patients had peptic ulcer which was proven to be only a manifestation of the underlying disorder. When it was corrected, another symptom took its place. Five of these seven patients suffered from muscle tension headache, and only two of them had extracranial vascular headaches.

The over-enthusiastic clinician is warned against trying to take away the helpful prop—headache is a social excuse and a very helpful device—lest the whole patient personality crumble in a fit of depression. The migraine patient has his attacks for two reasons: an inherited predisposition and a depletion of energy from any cause. Hirsch[74] determines this point to be the level of energy expenditure. He believes that migraine attacks restore energy to the body in the same manner that a convulsive attack restores blood sugar to a normal level. If the patient were able to compute his own ratio for efficient living, migraine attacks could easily be prevented. Relief for migraine, according to this author, should be based upon three features: (1) removing avoidable or unavoidable causes wherever possible; (2) treatment for increasing energy reserve; and (3) individual supportive therapy.

The incidence of migraine in pediatric practice is less than 1 per cent according to Glaser.[56] The major symptoms of migraine in children and adults are very similar, but the younger the child the more likely he is to have abdominal signs, such as nausea or vomiting. Cyclic vomiting of infancy may be a precursor of migraine. This author presents five case reports in which food allergy was thought to be a definite cause of migraine in children. He considers the possibility of inhalant origin of some of these attacks. The most common offending foods in childhood migraine are chocolate, egg, milk and wheat. With dosage adjustments, the same medications are used to relieve childhood attacks as has been reported beneficial in adults.

HEADACHE RELIEF

Friedman[53] believes that both physical and emotional factors are involved in the production of migraine. The most effective symptomatic treatment according to this author is the oral or rectal use of ergotamine tartrates and caffeine. Many failures with this preparation result from too low dosage or too late administration. The prodomal period, immediately after the onset of the headache, is the best time for administration of the drug. Amazingly consistent and dramatically rapid gratifying results with injectable Dramamine® have been reported by Vaisberg.[161] In each attack of migraine there was complete subsidence of the nausea with total relief of the pain within a matter of four minutes. The drug was given intravenously. The dose varied from 50 to 100 mg. Each of these fifty patients had had a definite history of migraine with a psychosomatic background and environmental "trigger mechanism" for precipitation of an attack. The patients to whom Dramamine-injectable was given had been suffering with severe headache for as long as two to six or more hours. In no instance did Vaisberg find a therapeutic failure with the use of this preparation. There were no undesirable side-effects. No matter how severe the attack, no matter how long its previous duration, Dramamine-injectable when given intramuscularly or intravenously proved to be a potent, non-toxic, well-tolerated form of medication for the relief of migraine.

Bellergal® proved to be of value in the prophylactic and interval treatment of a variety of headaches. Steele[145] selected a group of forty-five patients suffering from recurring headaches. Many of these patients had headaches of allergic type including variants and combinations. Eleven patients had migraine with these features predominating over the allergic or tension factors. The initial dosage of Bellergal was one tablet before each meal and at bedtime. The drug was withdrawn one week out of every four or six in instances where prolonged treatment was necessary. As time progressed, treatment was reduced to the smallest effective daily amount. Satisfactory results were obtained in 73 per cent of these instances in which this preparation was used. The single patient in this series with histaminic cephalalgia received fair results from Bellergal therapy. This author feels that it is necessary to pay attention to the interval inhibition of increased autonomic activity in attempting to relieve persistent headache problems.

Rectal suppositories or ergotamine tartrate and caffeine were highly effective in relieving migraine when employed by Graham.[61] Better results were obtained by rectal administration of this preparation than when Cafergot® tablets were given by mouth.

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1320 Second Ave. S. E.

Convention Echoes

The Eleventh Annual Congress of the College was held this year in Chicago at the Morrison Hotel, from April 25 through April 30. Following the long-established custom of the College, the Scientific Program was again preceded by the annual Graduate Instructional Course in Allergy, held on Monday, Tuesday and Wednesday, April 25, 26 and 27. This Course was under the supervision and direction of Dr. Orval Withers of Kansas City, as Chairman, and Dr. Morris A. Kaplan of Chicago, as Co-Chairman, both of whom had put in a great deal of hard work and effort to make it a success. By reason thereof they were able to assemble an exceptionally capable faculty of instructors and the Course was generally pronounced by those who participated therein as one of the most successful ever held.

Noon-day luncheons were held each day. On Monday the guest speaker was Smith Freeman, M.D., Professor of Biochemistry and Chairman of the Department of Biochemistry, Northwestern University Medical School, Chicago, Illinois, whose subject was "Steroids, Stress and Adaptation in Allergy." On Tuesday the guest speaker was Andrew L. Banyai, M.D., Past President, American College of Chest Physicians; Associate Clinical Professor of Medicine, Marquette University School of Medicine, Milwaukee Wisconsin, whose subject was "Treatment of Emphysema Secondary to Bronchial Asthma." On Wednesday the guest speaker was Fred W. Wittich, M.D., Minneapolis, Minnesota; President, International Association of Allergology, and Secretary-Treasurer of the College, whose subject was "Respiratory Allergies and Their Modifications in Patients Over 45 Years of Age."

The Program Committee was composed of Dr. Lawrence J. Halpin, Cedar Rapids, Iowa, Over-All Chairman, Dr. Homer E. Prince, Houston, Texas, and Dr. Fred W. Wittich, Minneapolis, Minn., with Dr. Giles A. Koelsche, Rochester, Minnesota, as consultant.

A total of fifty-three technical exhibitors occupied booths where products relating to allergy and allied subjects were on display. There were also eight scientific exhibits set up in the Constitution Room.

The eleventh General Session convened on Thursday morning, April 28, in the Constitution Room, with Dr. Merle W. Moore, of Portland, Oregon, presiding. The address of welcome was delivered by Dr. Max Samter, President of the Chicago Allergy Society, to which Dr. Homer E. Prince, President of the College, gave a brief response.

The guest speaker at the noon-day luncheon was Dr. Harry Alexander, Professor Emeritus of Clinical Medicine, Washington University Medical School, St. Louis, Missouri, who spoke on "Death from Asthma."

At the Friday afternoon session, also held in the Constitution Room, Dr. Homer E. Prince delivered his Presidential Address. This was followed by the introduction of Dr. Lawrence J. Halpin, President-Elect, after which the guest speaker, Dr. Robert A. Cooke, Director, Institute of Allergy, Roosevelt Hospital, New York, New York, spoke to the assembly on the subject "Medical Research in the Field of Allergy."

Following Dr. Cooke's address a short recess was held, after which the members assembled for the 1955 annual business meeting of the

College. At this meeting the following officers were elected for the ensuing year:

President-Elect—Dr. Ethan Allan Brown, Boston, Mass.
1st Vice President—Dr. John D. Gillaspie, Boulder, Colorado
2nd Vice President—Dr. A. M. Targow, Los Angeles, California
Secretary-Treasurer—Dr. Fred W. Wittich, Minneapolis, Minn.

The following Regents were also elected for a three-year term:

Dr. Philip M. Gottlieb, Philadelphia, Pa.
Dr. Stanislaus H. Jaros, Harlingen, Texas
Dr. Cecil M. Kohn, Kansas City, Mo.

The new Board of Regents of the College is now composed of the following members:

Susan C. Dees, M.D., Durham, North Carolina (term expires in 1957)
Jerome Glaser, M.D., Rochester, New York (term expires in 1956)
Philip M. Gottlieb, M.D., Philadelphia, Pa. (term expires in 1958)
S. H. Jaros, M.D., Harlingen, Texas (term expires in 1958)
Morris A. Kaplan, M.D., Chicago, Ill. (term expires in 1956)
Giles A. Koelsche, M.D., Rochester, Minn. (term expires in 1956)
Cecil M. Kohn, M.D., Kansas City, Mo. (term expires in 1958)
James A. Mansmann, M.D., Pittsburgh, Pa. (term expires in 1957)
James E. Stroh, M.D., Seattle, Wash. (term expires in 1957)
L. J. Halpin, M.D., Cedar Rapids, Iowa (President)

Dr. Giles Koelsche, as Chairman of the College component of the Joint Committee on Certification (upon which the Academy and the College are equally represented), delivered a report on the activities of the Joint Committee. He called attention to the fact that both the Board of Directors as well as the Board of Regents of the College, had, in the 1955 annual meetings just held, adopted resolutions instructing the Committee on Certification to continue its efforts to obtain separate certification in allergy within the framework of the Advisory Board for Medical Specialties. Following a discussion in which various members asked for and were given the floor, a resolution was unanimously adopted commending Dr. Koelsche and his Committee for their efforts to date, and endorsing and approving the establishment of a separate Board of Allergy within the framework of the Advisory Board for Medical Specialties.

The splendid cocktail hour, annually sponsored by the Schering Corporation of Bloomfield, New Jersey, with George Babcock, Jr., M.D., Associate Director, Division of Clinical Research, acting as host, was held on Thursday evening from six to seven o'clock, preceding the annual banquet in the beautiful air-conditioned Terrace Casino. Drs. Morris A. Kaplan and Leon Unger presented a most excellent program of entertainment which delighted all who attended. Sparkling burgundy was again served through the courtesy of Nepera Chemical Company of Yonkers, New York. Dancing followed the banquet.

The first annual meeting of the Women's Auxiliary was held on Thursday morning, April 28, in the Hollywood Room of the hotel, with the President, Mrs. Morris A. Kaplan, presiding. Mrs. Kaplan discussed the aims and purposes of the Auxiliary, and stated that she hoped the activities of the group would parallel those of the College and thus broaden the scope of its work, and that the success of such a program would be contingent upon hard and intensive work by all members. As its first

evidence of constructive accomplishment the Women's Auxiliary, by unanimous action of its membership, voted to make a contribution of $500 from funds in its treasury to the American Foundation for Allergic Diseases.

The annual meeting of the Women's Auxiliary was followed by a luncheon in the Cotillion Room of the hotel. Later refreshments were also served to all members of the College and their wives in Parlor B through the courtesy of the Chicago Allergy Society.

The new Board of Regents held its first meeting with President Lawrence J. Halpin, presiding, in the Walnut Room on Saturday morning, April 30, at 8:30 A.M. One of its first acts was to approve the selection of the Hotel New Yorker in New York City as the site for the Twelfth Annual Congress in 1956.

The Over-all Program Chairman chosen for the ensuing year is Dr. Ethan Allan Brown, with Drs. Lawrence J. Halpin and Fred W. Wittich as members of that Committee, and Dr. Giles Koelsche again acting as consultant. The Instructional Course Chairman is Dr. Morris A. Kaplan, with Dr. Howard G. Rapaport as Co-Chairman. Dr. M. Murray Peshkin was selected as chairman in charge of local arrangements and publicity.

The Nominating Committee selected this year consists of Dr. Lawrence J. Halpin, Chairman, Drs. Morris A. Kaplan, Dr. Giles A. Koelsche, Dr. John H. Mitchell and Dr. Harry L. Rogers.

The Twelfth Annual Congress and Graduate Instructional Course will be held at the Hotel New Yorker in New York City, April 15 to 20, 1956. This means that in 1956 for the first time the Annual Meeting will convene on Sunday and close on the following Friday noon, with the Instructional Course being held on Sunday, Monday and Tuesday, and the General Session on Wednesday, Thursday and Friday.—E.B.

THE AMERICAN COLLEGE OF ALLERGISTS FELLOWSHIP REPORT

The College is pleased to announce the names of those who have been elected within the past year to Honorary Fellowship, promoted to Fellowship, and accepted as new Fellows, Associate Fellows, and Corresponding Fellows:

Honorary Fellow

Edwin Sidi, M.D., 67 Boulevard Lannes, Paris XVI, France

Promotions to Fellowship

Bloom, Samuel, M.D., 9538 Kings Highway, Brooklyn, New York
Charlton, John D., M.D., Duke Hospital, Durham, North Carolina
Colby, Edmund D., M.D., 855 Union Street, Schenectady, New York
Egbert, Galen S., M.D., 919 The Alameda, San Jose, California
Eisenberg, Samuel H., M.D., 1727 South Main Street, Akron, Ohio
English, Frank A., M.D., 309 West Alameda Avenue, Roswell, New Mexico
Fox, Louvane A., M.D., Keene Clinic, Keene, New Hampshire
Hale, Ralph, M.D., 1418 Bryant Building, Kansas City, Missouri
Mechanek, Isidore, M.D., 41-24 43rd Street, Long Island City, New York
Moore, Irvin, M.D., 5013 France Avenue S., Minneapolis, Minnesota
Skinner, Durward A., M.D., 25 East Locust Street, Newark, Ohio
Sugihara, Clarence Y., M.D., 1010 South King Street, Honolulu, Hawaii
Sussman, Arthur, M.D., 345 Bloor Street West, Toronto, Ontario, Canada

Fellows (New Members)

Anthoulis, Demetrios, M.D., 107 Solonos Street, Athens, Greece
Grater, William C., M.D., 1620 Medical Arts Building, Dallas, Texas
Johnstone, Douglas E., M.D., 215 Meigs Street, Rochester, New York
Malloy, Connolly J., M.D., 1509 Sherbrooke Street W., Montreal, Quebec, Canada
Marks, Meyer B., M.D., 311 Lincoln Road, Miami Beach, Florida
McCausland, Alexander, M.D., 2622 Nottingham Road, Roanoke, Virginia
Nelson, Lloyd S., M.D., 616 LaSalle Building, Minneapolis, Minnesota
Preston, Edwin P., M.D., 518 Dupont Building, Miami, Florida
Ressetar, Michael J., M.D., 473 Lexington Avenue, Clifton, New Jersey
Tuft, Harold S., M.D., 3447 West 19th Avenue, Denver, Colorado

Associate Fellows

Arnow, Davis I., M.D., 1130 East McDowell Street, Phoenix, Arizona
Avren, Stanley, M.D., 1216 Douglas Street, Vancouver, British Columbia, Canada
Burns, William J., M.D., 1128 State Street, Schenectady, New York
Carrozella, John, M.D., 35 South Main Street, Wallingford, New Haven, Connecticut
Chervinsky, Paul, M.D., 56 Rotch Street, New Bedford, Massachusetts
Clancy, Robert E., M.D., 75 Bay State Road, Boston, Massachusetts
Dann, Alfred H., M.D., 2425 Geary Boulevard, San Francisco, California
Dean, George W., M.D., 425 East Wisconsin Avenue, Milwaukee, Wisconsin
Dolph, Ivar E., M.D., 205 South 4th Street, Chillicothe, Illinois
Fogelman, Hyman, M.D., 1104 Elder Avenue, Bronx, New York
Ford, William T., M.D., 460 Market Street, Williamsport, Pennsylvania
Gaul, L. Edward, M.D., 509 Hulman Building, Evansville, Indiana
Gauntt, William C., M.D., 1103 Nueces, Austin, Texas
Gittelson, George, M.D., 123 SW 37th Avenue, Miami, Florida
Hauser, William P., M.D., 1206 South 11, Bldg. 17, Tacoma, Washington
Jackson, Richard H., M.D., 808 Caroline, Houston, Texas
Kamin, Peter B., M.D., 5703 Fraser, Galveston, Texas
Kaplan, Seymour H., M.D., 50 South Middle Neck Road, Great Neck, New York
Kobrin, Meyer W., M.D., 729 Broadway, Gary, Indiana
Korn, Jerome M., M.D., 2119 West 5th Avenue, Gary, Indiana
Latham, Raymond W., M.D., 231 West 47th Street, Kansas City, Missouri
Lerner, Mary F., M.D., 1320 Union Street, Brooklyn, New York
Maged, Alan, M.D., 104 Lafayette Avenue, Suffern, New York
Milella, Nicola, M.D., 70, via Piccinni, Bari, Italy
Miller, Joseph B., M.D., 904 Dauphin Street, Mobile, Alabama
Morgenbesser, Howard D., M.D., 479 Empire Blvd., Brooklyn, New York
Morris, Hyman R., M.D., 2401 West 6th Avenue, Gary, Indiana
Owsley, Guy A., M.D., 214 North High, Hartford City, Indiana
Perez, Eduardo R., M.D., Lafayette Hospital, Arroyo, Puerto Rico
Powell, Clifford P., M.D., 3608 Clairmont Avenue S., Birmingham, Alabama
Robins, George M., M.D., 1735 North Wheeler Avenue, Portland, Oregon
Roth, Alexander, M.D., 411 Nichols Road, Kansas City, Missouri
Ryan, Hubert J., M.D., 504 Broadway, Gary, Indiana
Saferstein, T. Harry, M.D., 209 Physicians-Surgeons Building, St. Joseph, Missouri
Schafer, Walter L., M.D., 401 North Emporia, Wichita, Kansas
Scherr, Merle S., M.D., North Building, 1029 Virginia St. E., Charleston, West Virginia
Schirmer, Roy E., M.D., 100 North 6th, Fort Smith, Arkansas
Stephens, Lowell R., M.D., 600 East Liberty Street, Covington, Indiana
Strem, Edward L., M.D., 711 Lowry Medical Arts Building, St. Paul, Minn.
Vedder, James S., M.D., 650 South Central Avenue, Marshfield, Wisconsin
Wilhelm, Rudolf E., M.D., Brooke Army Medical Center, Ft. Sam Houston, Texas
Wood, Benjamin J., M.D., 165 Euclid Avenue, Sharon, Pennsylvania
Wygant, Edgar G., M.D., 1654 Oak Street, Chicago Heights, Illinois

Corresponding Fellows

Cortes, Jose Luis, M.D., Tlacotalpan 109, Mexico DF
Subiza Martin, Eliseo, M.D., Hermanos Miralles 73, Madrid, Spain

WOMEN'S AUXILIARY OF THE AMERICAN COLLEGE OF ALLERGISTS, INC.

Post-Convention News

The First Annual Convention of the Women's Auxiliary was held at the Morrison Hotel, Chicago, April 25-30, 1955, and was very successful. It was a gala get-together, where old friends and new friends mingled in the spirit of oneness. Now, more than ever, they had a common bond. The enthusiasm of the members was infectious and gratifying, and the identification badges were worn with pride—pride in the accomplishments of the first busy and fruitful year of the Women's Auxiliary. In one year we had received our Charter of Incorporation, secured 215 charter members, and completed the By-laws.

At our first annual business meeting on Thursday, April 28, 1955, the By-laws were approved, and the following members were elected to a three-year term on the Board of Governors:

Mrs. William H. Browning
Mrs. John D. Gillaspie
Mrs. John H. Mitchell

Mrs. Harry L. Rogers was appointed to fill the vacancy on the Board of Governors that was created when Mrs. Orval R. Withers accepted the position of Parliamentarian.

The Board approved the design for our corporate seal as submitted by Mrs. Johnny A. Blue. It further approved that a contribution of $500 be sent to The American Foundation for Allergic Diseases Our contribution to this worthy cause was applauded by the College.

The Local Committee outdid itself in providing for the comfort and entertainment of the visiting doctors and their wives. In addition to the teas, luncheons, tours and cocktail parties, the committee arranged for a glorious banquet complete with wines, gifts, orchids, a superb floor show and delicious food. We shall long remember the events of the convention week.

Our Auxiliary has made tremendous headway, and there is no limit to the assistance we can give to the College. As we begin our second year, ten new names have been added to our roster. If you are not a member of the Auxiliary, won't you become one? Information may be obtained by writing to:

Mrs. J. Warrick Thomas, Secretary, 4104 Cambridge Road, Richmond, Virginia.

We pay tribute to the memory of two of our Charter Members who passed away during the year.

Mrs. Alexander R. Altose
Mrs. S. E. Eisenberg

Our heartfelt sympathy to their families.

Mrs. Morris A. Kaplan, *President*
Mrs. J. Warrick Thomas, *Secretary*

ANNALS GUESSING CONTEST

Much interest was shown in the contest for guessing the number of words in the jumbled pages taken from ANNALS OF ALLERGY at the booth of the publishing house during the Chicago convention. Winner of the prize, a coffee server and warmer donated by the Bruce Publishing Company of Saint Paul, was Dr. Harold Oberfeld of South Milwaukee, Wisconsin, who came nearest to the number of 1077 words with a guess of 1100.

Runners-up in the contest who came within 60 words of the actual count were Dr. Milton Millman, San Diego, California (1020); Dr. M. A. MacDonald, Kalamazoo, Michigan (1120); Dr. Louis Kreindler, Cincinnati, Ohio (1125).

BOOK REVIEWS

THE CARE OF THE AGED (GERIATRICS). Sixth edition. By Malford W. Thewlis, M.D., Director, Thewlis Clinic, Wakefield, R. I.; Founder and Permanent Secretary, American Geriatrics Society; Special Consultant, Rhode Island Department of Public Health. 832 pages. St. Louis: C. V. Mosby Company, 1954. $15.00.

This sixth edition, the first edition of which appeared thirty-five years ago, is the work of a physician whose life work has been the ambulatory and hospital care of the aged. He is particularly equipped by a unique situation to set forth in a very practical manner the care of elderly persons. This volume covers the experiences of his clinic in a small town with a more or less fixed population, and where his work and that of his two uncles cover seventy-five years. The intimate knowledge of local families has been extremely helpful in studying patients from the cradle to the grave, which is so important in understanding the successive steps in the progression of a disease. Since most of his patients were of limited means, every effort was made to provide adequate care using practical but inexpensive methods of diagnosis and treatment. Careful history taking occasionally eliminated the necessity of numerous laboratory studies, and the author's portable laboratory, for use in x-ray, blood counts, chemical studies, and electrocardiograph, helped relieve hospital crowding and lessened the cost of illness.

This book of 832 pages has been completely rewritten in this edition and new material has been added, such as training the geriatrician; the geriatrician himself; ambulatory treatment of the aged; side effects of drugs; economic conditions in old age; graphology, emotions and disease; use of cortisone, especially in surgery; unsuspected syphilis; coronary thrombosis in physicians; and rehabilitation. Investigative forms used in the author's clinic are included. There are thirty-nine chapters, dealing with general considerations, gerontology, medicolegal relations, miscellaneous geriatric problems, diseases of metabolism and endocrine disorders, infectious diseases and focal disorders, systemic pathologic conditions, and special topics. The chapter on allergy under special topics is a fundamental consideration of allergic diseases in general.

Each chapter is followed by a list of references. The illustrations and printing are excellent. Every physician interested in the care of the aged will find this book valuable in his practice.—F.W.W.

SANDOZ ATLAS OF HAEMATOLOGY. Written and compiled by Dr. E. Undritz, Sandoz Pharmacological Research Laboratories, under the direction of Prof. E. Rothlin, and translated into English by Dr. A. M. Woolman. 179 pages. Basle, Switzerland: Sandoz, Ltd., printed by Frobenius Ltd., Basle, 1952. Price $7.00.

This very handy loose-leaf atlas is durably bound for a working desk reference.

Part I deals with general considerations, and is further subdivided into four sections. Section 1 deals with the fundamental principles of hematology, including terminology, classification of the blood cells into groups, species and stages of development; blood corpuscles under normal and abnormal conditions; cellular elements occurring in bone marrow films and not belonging to the hemopoietic systems; and the polyploidy of the blood cells. Section 2 deals with the technique of blood and bone marrow examination, including a table and text covering the various staining methods and their applications. This part alone is a valuable addition to any

laboratory, whether hospital, clinic, or of the private physician. Section 3 illustrates the forms for recording the results of blood and bone marrow examinations, and the fourth section presents the normal values obtained on blood and bone marrow examinations, including sedimentation rates, hemoglobin estimation, color index, hemoglobin concentration, color coefficient, saturation index, including formulas for each, also a chart showing the relative bone marrow picture, a chart giving the blood picture for children up to eight years of age and for adults, and a list of the chemical constituents of blood.

Part II is headed "Systematic Survey of the Morphology of the Blood Corpuscles," and includes tables for the differentiation of mature leukocytes and for the differentiation of the stem cells of the blood corpuscles; classification of the erythrocytes; the erythocytes under abnormal conditions; the normocyte and megalocyte systems; classification of the leukocytes; the systems of the blood basophils, eosinophils, neutrophils, monocytes, lymphocytes, plasma cells, megakaryocytes and platelets; blood parasites, et cetera.

Part III is an illustrated section with explanatory notes. The color photographs are superb illustrations of all the known blood and bone marrow diseases, including excellent photomicrographs of the blood parasites as seen in blood smears. At the end there is a most comprehensive list of references to the textbooks and manuals of hematology and references to publication of cases illustrated by figures. There is also a very complete index.

Medical students from the very beginning of their courses, laboratory technicians, laboratory directors, medical directors, as well as all physicians interested in the diagnosis of blood diseases should not be without this atlas. The loose leaf feature is most attractive, since the book can always be brought up to date by supplemental pages or sections. This atlas is made available at cost, as a service to the medical profession, by Sandoz Ltd., Basle, Switzerland,—F.W.W.

POTASSIUM METABOLISM IN HEALTH AND DISEASE (Modern Medical Monographs). Howard L. Holley, M.D., Department of Medicine, and Warner W. Carlson, Ph.D., Department of Biochemistry, University of Alabama Medical-Dental Schools, Birmingham, Alabama. 131 pages. New York: Grune & Stratton, 1955. Price $4.50.

This monograph presents an up-to-date review of the subject of potassium metabolism, and is intended to serve as a clinical guide in the diagnosis and treatment of abnormalities in potassium balance.

Knowledge of the role of the potassium ion in metabolism is still in its infancy, although its importance has long been recognized. Determination of the concentration of this important cation in body fluids by the relatively easy flame photometric method has revived interest in the subject. The essential role of the potassium ion in animal metabolism can be demonstrated in feeding experiments based on diets deficient in this mineral, which cause retardation of growth, paralysis of voluntary and intestinal musculature, degeneration of cardiac tissue, and finally death in laboratory animals, and these studies have been duplicated in humans.

The authors divide this monograph into three parts: (1) normal potassium metabolism, in which they discuss intra- and extracellular potassium; (2) potassium deficiency; and (3) potassium excess. The latter two sections deal with the etiology of extracellular potassium deficit and excess, the pathology of potassium deficiency and excess, signs and symptoms of hypo- and hyperpotassemia, laboratory findings, and treatment of both deficiency and excess of potassium.

A series of important appendices deals with the units used in body fluid measurements, the use of diet in the treatment of abnormal potassium metabolism (which contains sample low and high potassium diets, together with a list of the potassium

content of common foods, expressed in milligrams of potassium per 100 grams of food), and a listing of the sodium and potassium content of public water supplies of a number of the larger cities of the United States expressed in milligrams per 100 cc of water. There is a list of forty-one references, which the authors admit is representative of the literature rather than complete. The book is well indexed.

This monograph should appeal to all physicians interested in this vital subject.—V.E.S.

ANTIBIOTICS ANNUAL, 1954-1955. Edited by Henry Welch, Ph.D., Director, Division of Antibiotics, Food and Drug Administration, Washington, D. C., and Felix Marti-Ibanez, M.D., International Editor of *Antibiotics and Chemotherapy*, Vice President, Medical Encyclopedia, Inc., New York, N. Y. 1154 pages, illus. New York: Medical Encyclopedia, Inc., 1955.

Continued development of new antibiotics and improvement of those already established is evidenced in the *Antibiotics Annual, 1954-1955.* This volume of 1154 pages represents the proceedings of the Second Annual Symposium on Antibiotics which was held in Washington, D. C., last October, sponsored jointly by the U. S. Department of Health, Education, and Welfare, Food and Drug Administration, Division of Antibiotics, and the journal *Antibiotics and Chemotherapy.*

There were 250 participants in this conference, who presented 172 reports which are printed in the present volume. Each one has tables, figures, and a bibliography on the particular subject at the end of the paper. Fourteen new antibiotics are described in carefully controlled studies, and reports on the use of antibiotics in human nutrition will undoubtedly open up new fields of usefulness for these drugs. No new antibiotic has yet been found which is effective against the small viruses and cancer, but two antibiotic substances (puromycin and actinomycin) are described which have antitumor and anticarcinogenic effects. There is an excellent historical background of the antibiotics presented by Selman A. Waksman.

The subject matter of this volume is too varied to allow any detailed description of the contents. It represents both investigative and clinical studies. It should be read by all physicians who use antibiotics and kept handy as a reference book.—F.W.W.

GROUP ON "ALLERGY OF THE NERVOUS SYSTEM" FORMED

On April 27, 1955, during the annual congress of the American College of Allergists, a group of members of the College interested in allergy of the nervous system met to discuss this subject. Present were: Dr. Theron Randolph, Dr. Susan Dees, Dr. S. H. Jaros, Dr. Harry Clark, Dr. P. M. Gottlieb, Dr. C. R. Ahroon, Jr., Dr. Milton Millman, Dr. G. S. Frauenberger, and Dr. Frederic Speer. Dr. Randolph was named president of the group, and Dr. Speer was elected secretary. The principal business of the meeting was a discussion of nomenclature in this field. It is planned to assemble an outline of history and bibliography in nervous system allergy. The group plans informal meetings to be held at the time of the annual sessions of the College.